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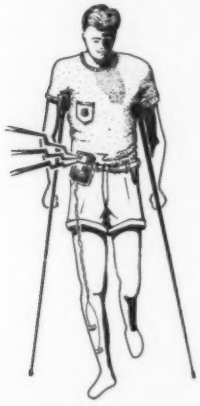

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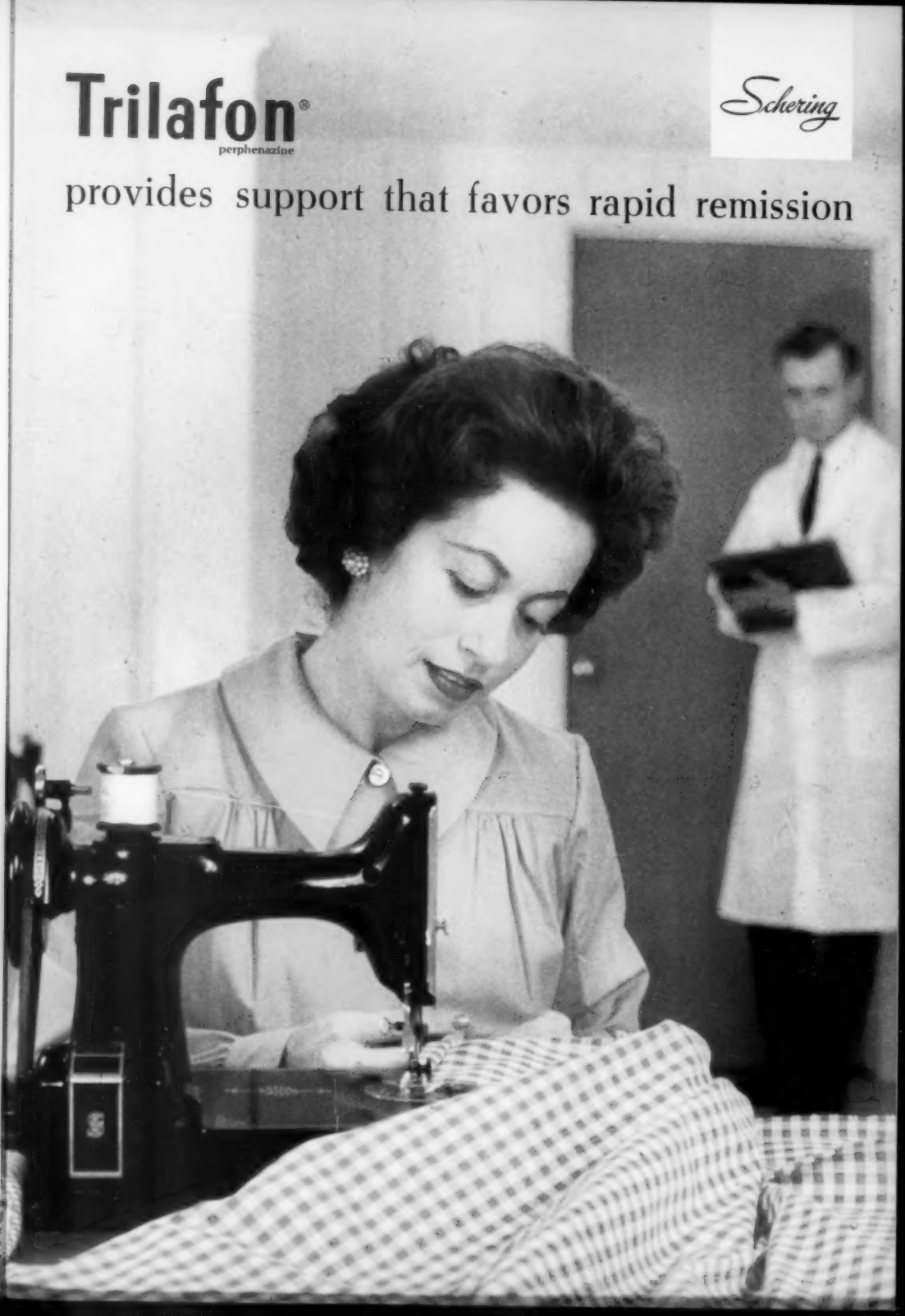

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Neurology Volume 11 • Number 9

The Robert Wartenberg Memorial Lecture

Testamentary capacity in aphasia

Macdonald Critchley, M.D.

THERE IS A PROBLEM in legal medicine which knocks importunately at the doors of clinical practice, cutting right through the tangled undergrowth of metaphysical and psychologic argument, for it brings the neurologist right out into the open forum of the jurist. Here meet the two disciplines of law and medicine, and whether communication be achieved or not depends in part upon the neurologist's sympathetic understanding of the problem.

The question in short concerns the testamentary competency of a dysphasiac subject. At any moment, a neurologist may be confronted with this medicolegal conundrum and even be required to declare and substantiate his opinions in a court of law. In such circumstances, it might transpire that a conflict of attitude develops between the neurologic conception of what lies within the intellectual compass of a particular dysphasiac and the accepted precedents of the lawyer. On the whole, the attorney inclines to take an oversimple view by merely ignoring the clinical difficulties.

The literature of both the law and neurology proves to be surprisingly unhelpful. The classic medical papers on this subject by du Saulle,[1] Bramwell,[2] and Edmunds[3] were published between sixty and seventy years ago. My own earlier study[4] dates from 1938. There has since been such progress in the study of aphasia, and there is so much more realization as to the complexities of the problem that the early papers can serve merely as signposts. We are now aware that disorder of speech is usually not an isolated feature but one which may be accompanied by a considerable change in mentality or behavior. But for all our modern ideas, the practical problem of assessing an aphasiac's fitness to make a valid will is none the easier. We may bear in mind, however, that the appraisal of testamentary capacity is more likely to yield to a common-sense line of enquiry than to undue excursions into philosophy or psychology. This particular medicolegal problem is actually a duplex one. First, there is the question of the validity of a will which has already been drawn up. The aphasiac may die and leave a will which had been executed during his period of illness; the will may be contested, and the neurologist may then be consulted as to the state of the man's mind at the time in question. The second problem arises when an aphasiac patient wishes to

From The National Hospital, Queen Square, London.

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draw up a will or to add a codicil. The doctor may then be asked whether his patient really is capable of intelligently advising or executing the drawing up of a will. In the one case, the will is produced as a fait accompli and nothing may have been known of its execution during the patient's lifetime. The neurologist may have only his notes and his recollections to support his opinions as to testamentary ability. In the other case, the neurologist may have ample time to observe the mental state of his patient, with opportunities of obtaining second or third opinions in consultation. Moreover, he can make sure to be present at the time of the signature to determine that the patient really does understand the precise nature of the testament.

In either case, the neurologist may be called upon to uphold his viewpoint before a jury and to be subjected to cross-examination. Unwittingly, he may find himself in court not so much as a detached expert witness but almost a protagonist, taking an all-important part in supporting either plaintiff or defendant, and he might be set up counter to a neurologist on the other side of the dispute.

The question of capacity ultimately turns upon the integrity of the patient's mental state at the time of the signing of the will. The neurologist is confronted with the all too familiar question of whether aphasia per se entails an important detriment to a patient's cerebration, hindering intellectual operations to a significant degree. One does not need to stress the difficulties of carrying out reliable nonverbal intelligence tests. No two cases of aphasia are exactly alike, and the proportion of available to unavailable language ties up with the nature and quality of the patient's thinking. Certainly, in many cases of speech defect, there does exist a definite affection of the general intellectual status, as well as obvious modifications in the total behavior. In such, not only is there an impaired comprehension on the part of the patient of what he hears or what he sees before him in writing, but judgment, recollection, calculation, and abstract thought are also severely deranged. In such cases, there really occurs a minor dementia, and such patients are surely quite incapable of making a will.

It is often argued, however, that not all aphasiacs necessarily suffer a disorder of the internal process of thinking. There is available the evidence of those who have recovered from their aphasia and can recall in retrospect their state of mind when speech was still impaired. Dr. Samuel Johnson,[5] when afflicted with aphasia, tested his sanity by composing and offering up a prayer in Latin verse. One of Foster Kennedy's[6] patients, an eminent American statesman, was able to carry out his duties for half an hour after his stroke, thinking clearly about various topics, unaware of any mental disturbance; only later, when attempting to speak, did he discover his aphasia. Russell Brain's[7] patient, a solicitor of 78 years, with paraphasia and syntactic and nominal defects, was nevertheless able to comprehend abstract legal questions put to him concerning the nature of a contract. Despite the welter of muddled phraseology, it was obvious that he was giving the correct replies. At one time, it would have been said that aphasiacs most likely to preserve intact their processes of thought were those with a purely "motor" or "expressive" defect (with seemingly full appreciation of spoken and written speech) and especially those with "amnesic aphasia" (where the main difficulty lies in naming persons or objects). Such patients are often regarded as capable of making a valid will. But the antinomy of "motor" and "sensory" types of aphasia is wearing a little thin, thus adding to the present difficulties of coming to a medicolegal opinion.

Among the older aphasiologists, F. Bateman[8] (1890) devoted a chapter in his monograph to this forensic problem. He quoted the case reported by Billod of a man who, despite an aphasia, continued to serve as mayor and municipal councillor with apparent efficiency. He used his left hand for the purpose of writing, and, while still aphasiac, he drew up a holograph will which was subsequently upheld in a court of law. Joseph Collins,[9] writing in 1898, answered the question on the basis of his classification of the aphasias into "cortical" and "sub-cortical" types. Patients belonging to the former category are ordinarily not capable of will-making, while those in the latter class, that is, of "sub-cortical" aphasia, usually are capable of indulging in civil transactions. In the same year, Bastian,[10] mindful of the difficulties of this problem, contented himself by merely enumerating types of cases in which

the patient could not be expected to make a valid will. These comprised [1] cases of complete aphasia and agraphia; [2] cases in which complete word-deafness and word-blindness coexist; and [3] cases of "total aphasia." On the other hand, will-making might present no particular difficulty to patients with anarthria, "aphemia," or "pure word-blindness."

Nowadays, these classifications and terminologies are virtually meaningless, and, in now recognizing the complexities which underlie what would seem to be straightforward, we have increased materially our own difficulties.

In assessing testamentary capacity, one of the first tasks is to determine to what extent the patient understands printed and spoken language. The ability to say "yes" and "no" correctly is important but not crucial. An aphasiac need not necessarily be debarred from making a will when unable to say "yes" or "no" or when he says one of these while meaning the other. Much more important in such aphasiac subjects is the ability to communicate by means of clear and unequivocal gestures. The patient may articulate "no" when he means "yes," but his vigorous nodding of the head should leave no doubt as to what actually he desires to imply. Many aphasiac patients can make intelligible signs and can themselves understand movements of gesture and pantomime, even though this particular type of nonverbal communication is not wholly intact. In other words, restriction of vocabularly does not of itself preclude the patient from making a will.

What used to be called "mixed sensori-motor" types are the ones most likely to interfere with testamentary capacity. Those varieties in which the patient obviously does not understand what he hears and in which the speech has assumed the characters of "jargon-aphasia" almost certainly debar the patient from making a will. One type of sensory aphasia exists, however, in which testamentary capacity may possibly be intact, namely, the allegedly pure cases of alexia (word-blindness). Although the existence of any such type is nowadays regarded with some skepticism, neurologists will agree that a difficulty in comprehending written or printed matter can at times dominate the clinical picture. It is in just such a case that disturbance of mentation is minimal. Foster Kennedy and Alexander Wolf[9] described an advocate who showed so little in the way of intellectual defect that he was able to plead a case in court eloquently, and yet he proved afterward to have been alexic at the time. An older observation is that of the distinguished Dean of the Medical Faculty at Montpellier, Professor Lordat,[11] who, on recovering from an alexic type of aphasia, wrote concerning his mental state, ". . . I did not experience any difficulty in the exercise of thought. Accustomed for so may years to literary studies, I congratulated myself on being able to arrange in my head the principal propositions of a lecture and on not finding any undue trouble in the alterations which I chose to introduce in the order of my ideas. The memory of events, principles, dogmas, abstract conceptions was as it had been during health."

I believe, however, that autobiographic accounts of mental operations made in retrospect by recovered aphasiacs are not altogether reliable. Hindsight does not necessarily entail insight. The factors of unawareness of disability, or denial thereof, are subtle ever-present mechanisms. Like the notoriously fleeting memory of physical pain, the recognition of past confusion is imperfect. Organic repression of the nature and intensity of cerebral defect is both powerful and enduring.

WHEN THE WILL HAS ALREADY BEEN MADE

The neurologist must realize that the law usually takes up the attitude that the very existence of a testament is an important argument in itself, one where the burden of disproof is very much the responsibility of the plaintiff who challenges its validity. The document is assumed to be in order unless proved to the contrary. The existence of a will implies that the testator knew at the time that he was making a will, that he was aware of the nature and extent of his property, and that he was cognizant of the natural recipients of his bounty. These were the propositions laid down in 1870 by Lord Chief Justice Cockburn. As Dr. Usden[12] has said in his valuable paper on "The Physician and Testamentary Capacity," "He should be prepared to accept the fact that all too often the courts neglect reputable medical testimony when it is contradictory to non-medical testimony. Case after case can be found where the court has paid absolutely no

attention to the opinions of the experts because the behaviour of the testator as detailed by lay witnesses pointed in the opposite direction."

Accordingly, when a neurologist is asked to pass opinion in restrospect as to the state of mind of a deceased aphasiac at the time the will was signed, at least 2 separate factors should be considered: [1] the will itself and [2] the testator. Is the will itself an intrinsically plausible one? Or has the patient disinherited his wife and family and left his money to an unlikely charity or an attractive newcomer? These matters, though more within the province of the lawyer, do throw light upon the workings of the mind and as such constitute important medical data. Is the will a simple one containing only 1 or 2 clauses, or is it an extremely long and complicated document? Obviously, the former might well have been within the capacity of the aphasiac when the latter certainly was not. Thus, an isolated piece of property or a modest sum of money distributed among 1 or 2 likely recipients could be looked upon as the product of judgment of a simple and straightforward kind. But where the property is considerable and complex and the testatees numerous, a competent will would entail a conception of magnitude and of mental exercises entailing division and other arithmetic manipulations. Such intellectual analyses would be expected to suffer in all but the mildest cases of aphasia. Abstract attitudes of thought, like creative cerebration, are too remote for attainment in the face of speech loss.

As to the testator, the neurologist will have to decide, from his notes or from his recollection of the case, not merely whether at the time in question the patient could have made simple affirmations or denials and in appropriate circumstances but also whether his mind was clouded, whether he had been correctly orientated in all spheres, and whether he could understand what others were trying to convey to him. It must always be remembered that some fluctuation in the intensity of the symptoms is not unusual with cerebral softening and that the patient may perhaps have been capable of making a will on one day and not on another or even only at certain times of the day. Lastly, the neurologist must recall whether there had been any noteworthy aberration of conduct or behavior during the aphasia.

The neurologist must also decide as to whether any gross or diffuse brain disease occurred, over and above the focal lesion responsible for the aphasia. Thus, cases in which there were evidences of diffuse cerebrovascular disease, or a history of multiple strokes, or faulty control over the sphincters should be regarded with grave suspicion from the standpoint of testamentary capacity. Although in itself advanced age is not regarded by the law as constituting testamentary incapacity, the combination of senility with aphasia should be held as suspect by the doctor. The nature of the concomitant neurologic signs may be of importance. The association of a hemiplegia with such epiphenomena as apraxia, hemianesthesia, and especially hemianopsia may be of serious import as indicating a particularly widespread destruction of brain tissue.

Paralysis of the hand that holds the pen does not of itself render the aphasiac incapable of making a valid will. As early as 1743, the Hanoverian law courts upheld a will made by means of signs by a citizen of Münden, who had been deprived of speech. The law, in England at least, has accepted such evidence as an affirmatory pressure of the hand, nodding, and graphic marks (Hill v. Jeffs, Judgment of Bargrave Deane J. 1913), even though neurologists today would look upon that particular decision with some dubiety. Where a testatrix commenced her signature but failed to complete it, the will was upheld, for it was ruled that she knew and approved the contents and meant to sign it (Chalcraft v. Giles 1948).

The law in England has taken cognizance of the unusual circumstance wherein a patient had discussed the disposal of his property and the general layout of his will and then suffered an aphasia. The testator could recollect that he had given instructions about his will but nothing more; he nevertheless believed that the will was executed in accordance with his wishes, and this limited degree of capacity was ruled valid (Perera v. Perera 1901).

WHEN NO WILL HAS YET BEEN MADE

If the aphasiac patient and his relatives are desirous fo. .. will to be executed de novo, a considerable responsibility falls upon the medical practitioner. The practitioner will be well advised not only to call in a colleague to as-

sist but also a consultant and a lawyer. Here it is that the neurologist should take command of the situation. It is better that all relatives, friends, and servants should be excluded from the consultation. If the proceedings prove to be rather lengthy and tiring for the patient, one must not hesitate to order an adjournment. The phenomenon of waning attention and also of extreme mental viscosity should be respected. Should the mental state be unsatisfactory at one particular time, it is possible that an improvement may occur within a few days, and all documents should be kept aside in readiness. In cases of aphasia due to cerebral tumor, temporary improvement can perhaps be obtained by means of hypertonic salt solution long enough to permit a valid testimony.

The will should be as simple and brief as possible, clearly typed out so as to afford the minimum difficulty to the patient if he can still read. Where only one straightforward clause is concerned (for example, when the wife or a son is the sole beneficiary), it is not strictly essential that the testator should know the precise total value of his estate. This becomes imperative, however, if there are a great many beneficiaries, with certain conditions demanded and with certain residual legatees.

First, it must be clear to all that the patient is desirous of making a will, and every fragment of speech and movement of gesture on the part of the patient must be accurately noted and recorded verbatim. The patient is then asked which person or persons are desired as beneficiaries. Having obtained a reply, one would do well to repeat this question back to the patient to be certain that no paraphasic error in naming has been made and also to suggest one or two additional and unlikely names, noting whether the patient now gives evidence of dissent. Care must be taken, however, to avoid confusing the patient by too many test questions, for will-making before an assembly is a tiring ordeal for a sick and aphasiac patient. One must also watch for the occurrence of verbal perseveration, whereby the same answer might be given to a succession of questions, contrary to the patient's intention.

If the property concerned is a considerable one and a simple one-clause will is impractical, one may adopt the method employed with success by Edmunds and upheld by an English court of law (Moore v. Moore 1900). This has become known to the legal profession as the "pack of cards" case. The physician, with the assistance of the patient's solicitor, prepared a large number of cards 5 × 4 in. in size, upon which were printed in bold type various categories of property to be bequeathed, of functions to be performed, and of numerous persons including relations, friends, and charitable organizations. These were placed before the patient, who slowly and deliberately chose certain cards. These were then marked and fastened together. Thus, the patient was shown the card denoting the largest item and at the same time was asked, "Whom do you give that to?" The patient then took the pack of cards containing the proper names and, after slowly turning them over, selected the one marked with the name of her brother. This procedure was then repeated until the property was disposed of. Thus, the doctor dealt the cards, the testatrix played them back, and the lawyer gathered the tricks. From the selected cards, the lawyer drew up an appropriate will in effective legal form. On the following day, the doctor and the solicitor read out the will slowly, and the patient signified concurrence clause by clause. A final assent was given, and the patient affixed her mark which was witnessed by both lawyer and doctor. On account of the magnitude of the estate, the will had to be "proved in solemn form," that is, in open court. After the various witnesses had been examined and cross-examined, the President, Sir Francis Jeune, expressed himself satisfied with the validity of the will (The Times, Feb. 13, 1900). Such a procedure, which of course can only be adopted when the patient has no disorder in the comprehension of printed matter, is open to one serious objection, namely, the possibility that some desired legatee or charity might be forgotten and therefore omitted from the proffered collection of names.

Whatever technic is adopted, it should be the endeavor to probe sympathetically and patiently so as to ascertain the fundamental wishes of the subject.

When the will has been made out by the lawyer and typed, it must be read over slowly to the patient. All must be satisfied that he understands and agrees with the contents.

Lastly, the patient must sign the will or affix his mark, this signature (or its equivalent) being witnessed by two others who must sign in his presence. In English law, these witnesses should be told that the document signed is the patient's will. They need not include the medical men nor the lawyer, but they should be responsible persons, not domestic servants. They need not know the terms of the will, and they must not be beneficiaries or executors.

A combined "private" report might well be drawn up by the practitioner, lawyer, and neurologist, read over and agreed, signed and witnessed, and safely filed along with the testament. The neurologist should preserve his copy against future contingencies.

UNDUE INFLUENCE

When judging a patient's capacity to make a valid will, there is a third point which may arise in addition to the problems of speech affection and intellectual capacity. It may be argued by the relatives and their legal advisers that the patient, by reason of his stroke, had lost full possession of his "will-power," had developed unreasonable likes and dislikes, and had become susceptible to undue influence in drawing up his will. Such a protest is to be expected when the terms of the will are surprising or disappointing. A disinherited wife or near relative may contest the validity of a will which names as beneficiary a comparative stranger or a charity. In at least one state, Louisiana, undue influence does not of itself invalidate a will, but, in most states and in English law, the factor of "undue influence" is an important consideration in judging the validity of a will. The court might well seek the doctor's opinion, though of course the decision as to the validity will rest with the judge and jury. No more difficult task lies before a medical practitioner than to express an opinion on such a matter. It must be remembered that mere propinquity of relationship does not necessarily constitute a moral claim upon a testator's actions. The relatives may have been rapacious, the wife a shrew, and the sons and daughters ne'er-do-wells; the patient's action in willing his property to a nurse, friend, or servant who had shown him kindness or to a charity with which he was in sympathy may not necessarily be evidence of an unsound mind. Fortunately for the practitioner's peace of mind, this dilemma is nowadays less likely to occur, for in England it is now impossible for a testator to leave his wife or next of kin entirely devoid of maintenance.

This vexed question of testamentary capacity in patients bereft of speech illustrates the fact that legal and neurologic thought are somewhat out of alignment. The lawyer thinks in terms of full competency versus total incapacity. On our part, we believe that there exists a sort of spectrum of intellectual accomplishment in aphasiacs which makes it unrealistic to try to answer the lawyer's naive enquiry as to whether a particular patient's will is or is not valid. Even among neurologists, there has been a subtle change in opinion. Today, I would say that fewer aphasiacs possess testamentary capacity than I thought was the case twenty-three years ago, that is, when I last considered this problem. In aphasia, an absolute integrity of intellectual function is the exception and not the rule.

But obviously the problem is one which cannot be judged in isolation. When Hughlings Jackson[13] was asked the same question, "Can an aphasic patient make a will?", he gave the Delphic reply, "Can a piece of string stretch across a room?" Today, we would give an answer in similar terms, but I would like to phrase my reply, "Can this piece of string stretch across this room? Probably not."

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Ultrastructural alterations in neurons of mice infected with MM polioencephalitis virus

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MORPHOLOGIC ALTERATIONS in nerve cells after infection with neurotropic or pantropic virus have been vigorously studied by light microscopists,[1–5] sometimes in correlation with histochemical technics and special optical methods.[6–9] In the last decade, enormous advances toward an understanding of virus multiplication and its relation to cellular metabolism have been made by virologists using a variety of chemical and physical technics.[10–16] Particularly fruitful has been the application of the electron microscope to the study of virus activity in tissue culture where direct visualization of intracellular virus growth and cytomorphologic changes can be carried out in relative simplicity because of the uniformity of cell type and lack of inflammatory reaction.[17]

Nonetheless, there are obvious differences between the biology of cells in tissue culture and in vivo,[18–21] some of which could be of importance in understanding virus-host relationships and the complexities of the virus diseases in the central nervous system. It was therefore considered of value to utilize the electron microscope to study experimental pathologic material prepared by infecting *living animals* with a highly virulent virus which regularly produces a severe polioencephalitis.[22] The present report will be chiefly concerned with nerve cell alterations, and the more general fine structural aspects of inflammation in the central nervous system will be reported separately.[23]

MATERIALS AND METHODS

White mice 3 to 6 weeks of age were injected subcutaneously with approximately 0.1 cc. of a 10^{-4} dilution of brain homogenate infected with pantropic rodent virus of the Columbia-SK group, MM strain.* No clinical signs were apparent until the second day, when the animals were notably less active, had roughened fur, and showed slight to severe weakness in the hind legs. On the third day, all animals were severely paralyzed with involvement of the fore as well as hind limbs, had definite respiratory difficulty, and appeared moribund. Animals were sacrificed at twenty-four, forty-eight, and seventy-two hours after infection. A coronal section was made through the skull and brain of the anesthetized animal; tissue blocks were removed from basal cortex, fixed in 1% buffered osmium tetroxide, dehydrated through graded dilutions of alcohol, and embedded in a mixture of methyl and butyl methacrylate. An important practical step in

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*Kindly supplied by Prof. C. V. Jungeblut of Columbia University in a 50:1 glycerin suspension. The virus underwent several hundred passages in mice in his laboratory and a few intracerebral and subcutaneous passages in our laboratory.

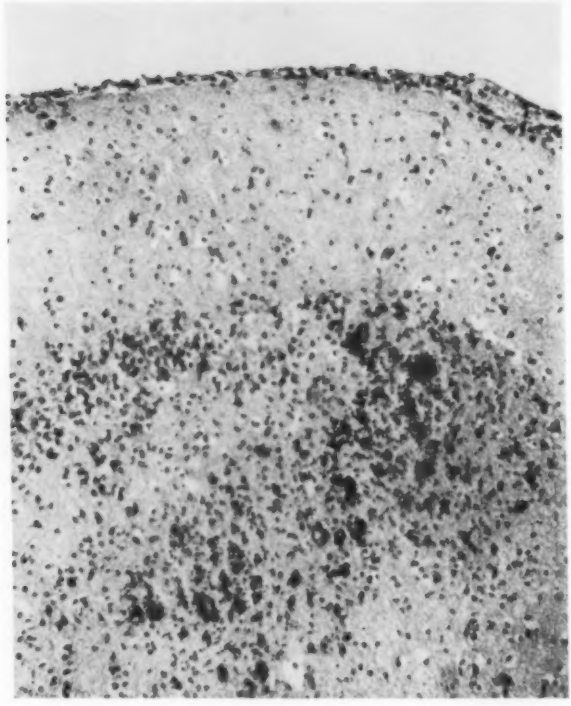


Fig. 1. Prepyriform cortex of mouse infected three days before sacrifice. Note particularly focal collections of cells which are often congregated around neurons. Both polymorphonuclear leukocytes and activated microglia are present, though former are much more numerous. Hematoxylin-eosin stain. × 170

these experiments was the determination of significant regions of the blocks by the examination of 2- 3-μ thick sections with the phase microscope. Ultrathin sections were then made from these areas with a Porter-Blum or Leitz microtome and examined in a Siemens ÜM 100 electron microscope.

Adjacent portions of the brain were fixed in 10% formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin or cresyl violet and studied with the light microscope.

That portion of the brain remaining after removal of samples for light and electron microscopy was frozen immediately after sacrifice of the animal. In an effort to correlate virus concentration and morphologic alterations, separate homogenates were prepared from the frozen brain pools of animals sacrificed at intervals of one, two, and three days. Subcutaneous injections of 0.1 cc. of 0.5 logarithmic dilutions of a 10% aqueous homogenate from each pool were made, using 4 mice for each dilution. Titers were expressed as negative logarithms of LD_{50}. These preliminary virologic studies demonstrated a low concentration of virus in the animals killed one day after infection, with no morbidity or mortality after injection with serial dilutions and only 2 deaths with injection of 0.1 cc. of the 10% homogenate itself (10^{-1} dilution). In the two-day group, there was a very significant titer of $10^{-5.55}$ LD_{50}. Homogenates of brains of animals sacrificed three days after infection showed a further rise of the virus titer to $10^{-7.66}$ LD_{50}.

Control animals were prepared by subcutaneous injection of uninfected brain homogenate. Material from these animals was also examined by light and electron microscopy, and its lack of pathogenicity was demonstrated by failure of these mice to show clinical symptomatology as well as negative results with homogenates from these brains in additional mouse passages.

A parallel series of mice was infected in the same manner and utilized for correlated and detailed virologic, light microscopic, and enzymatic studies. The results of these experiments will be reported elsewhere.[24]

RESULTS

With the light microscope, no pathologic alterations were seen in animals sacrificed twenty-four hours after inoculation with virus. In the cerebrum of animals killed on the second or third days, there was a severe, necrotizing polioencephalitis. Occasionally, minute scattered foci occurred in the dorsal cortex, but in all animals the lesions were much more severe and constant in the rhinencephalon, particularly in the prepyriform region. Many of the neurons had disappeared or were obscured by the intense polymorphonuclear infiltrate (Fig. 1). These leukocytes as well as reactive microglia were often collected in small groups around nerve cells which showed various degrees of necrobiosis (Fig. 2). Commonly, the neuronal cytoplasm was brightly eosinophilic and well demarcated from other structures; however, in later or more severe stages of destruction, it became vacuolated with irregular cell margins. Pyknotic and fragmented nuclei were numerous; some were neuronal in origin, although most of the basophilic bodies of varying sizes were the result of polymorphonuclear disintegration.

The ultrastructure of normal nerve cells has been described by several investigators,[25–28] and the appearance of a neuron from the control series is illustrated in Figure 3. With the electron microscope, varying degrees of neuronal damage were seen in animals sacrificed both two and three days after infection, but, as with the light microscope, no alterations were apparent in animals which were infected only twenty-four hours before sacrifice.

In the nuclei of neurons which were still structurally intact, there was occasionally a striking widening of the perinuclear space which was normally bounded by an inner and an outer membrane[25] (Fig. 4). Such a widening resulted in the formation of broad cisterns into which "islands" of cytoplasm protruded, indicating the irregular shape of these dilations. Filling these broadened spaces was a fine, moderately osmiophilic precipitate. Within the nuclei of other neurons which may or may not have shown definite cytoplasmic abnormalities, there occurred densely osmiophilic granules of varying sizes which in some cells were quite prominent (Fig. 5a and b) and in more severe stages of destruction formed small clusters (Figs. 6 and 7). The usual finely granular or reticulated chromatin in these definitely abnormal neurons formed fairly well-circumscribed aggregations with distribution marginally and as large islands within the nucleus. In such nuclei, the customary network of nuclear material might no longer be recognizable, and one saw granular elements of moderate density and relatively uniform size which could be easily distinguished from the densely osmio-

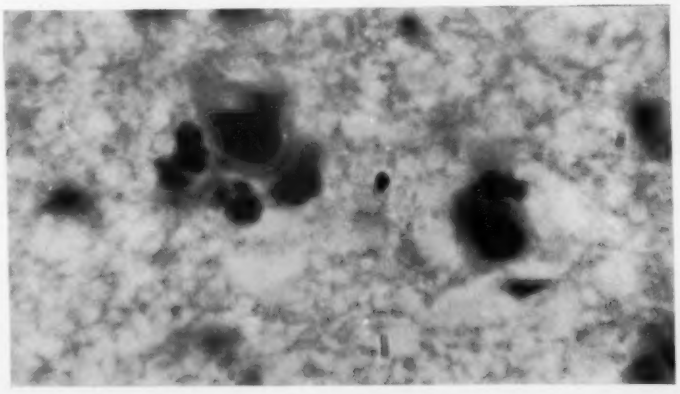


Fig. 2. Perineuronal accumulations of inflammatory cells. Nerve cell cytoplasm is brightly eosinophilic and somewhat vacuolated, with indistinct cell margins. Hematoxylin-eosin stain. × 1,500

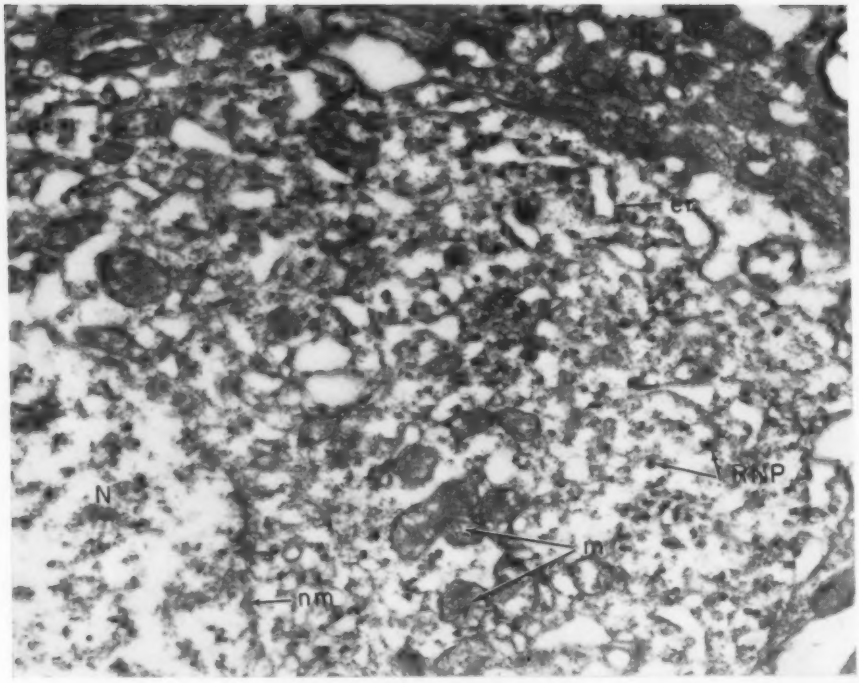


Fig. 3. Normal appearing nerve cell from control animal sacrificed three days after subcutaneous injection of uninfected brain homogenate. N=nucleus; nm=nuclear membrane; m=mitochondrion; er=endoplasmic reticulum; RNP=clumps of ribonucleoprotein granules. × 21,600

philic granules just described but were not so readily differentiated from the clumped islands of nuclear chromatin (Fig. 7). The nuclear membranes of such severely damaged cells were nearly always separated by a wider gap than usual, though extreme dilation of this space has been seen only in relatively well-preserved cells. Often, nuclear membranes were deeply infolded, and occasionally chromatin material lay outside the nucleus in the cytoplasmic debris (Fig. 7). No special changes in either the nucleolus or perinucleolar chromatin have been observed in any of the stages of neuronal disintegration.

Within the cytoplasm of nerve cells that were still relatively intact, the endoplasmic reticulum often appeared to be more prominent, and there was a marked increase in number and change in distribution of fine particulate components of the cytoplasm. Thus, many of the profiles of the endoplasmic reticulum were larger and more round and regular than normal (Fig. 5a and b), and there were numerous small, round particles of relatively uniform size which showed some variation in density (Figs. 5 and 8). These might be on the surface of the endoplasmic reticulum membranes, along the outer nuclear membrane, or embedded in the ground cytoplasm but showed no particular tendency toward arrangement in small star-like clusters as is characteristic for ribonucleoprotein granules in normal nerve cells (Fig. 3).

In most of these cells that showed moderate or severe changes, some of the mitochondria appeared abnormal. Their cristae were often clearly visible but lacked the customary transverse orientation. The density of the mitochondrial matrix was sometimes greater than usual, and irregular, often annular osmiophilic de-

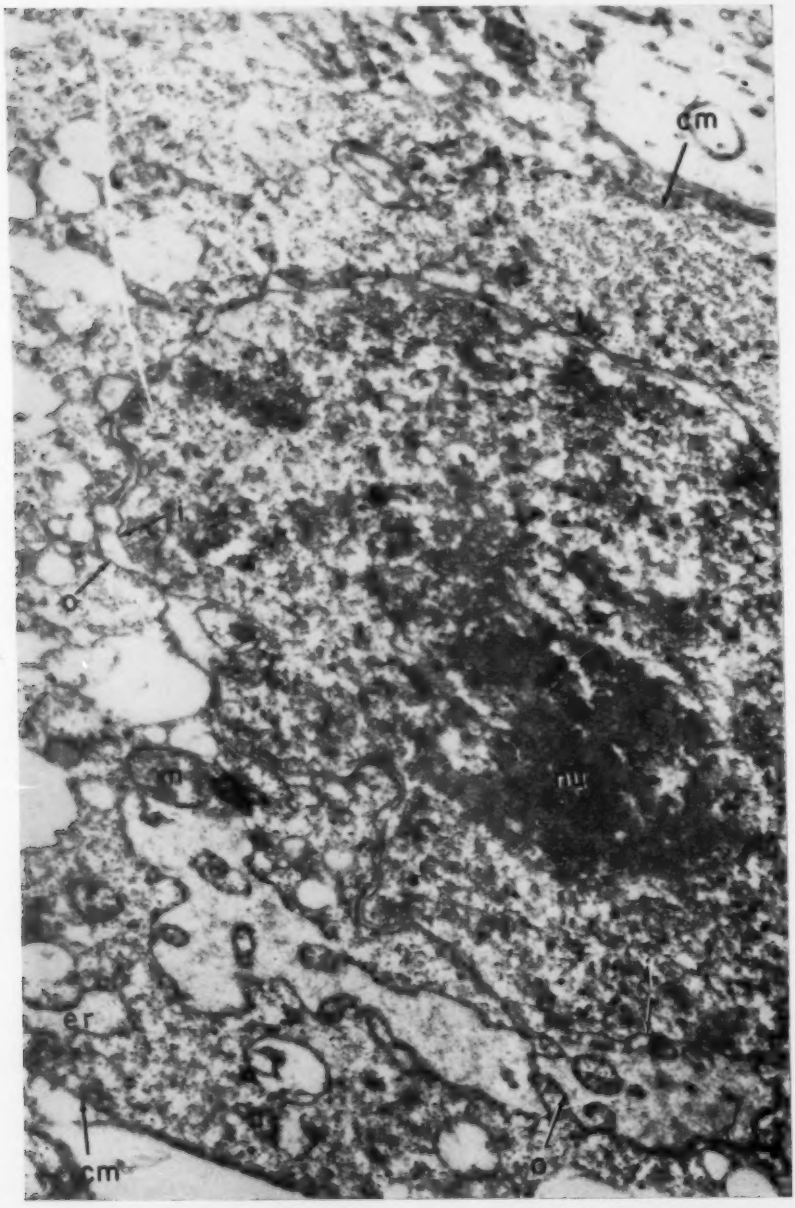


Fig. 4. Nerve cell which appears normal except for pronounced widening of space between inner (i) and outer (o) nuclear membranes of cisterns of endoplasmic reticulum (er). nu=nucleolus; m=mitochondrion; cm=cell membrane. × 21,600

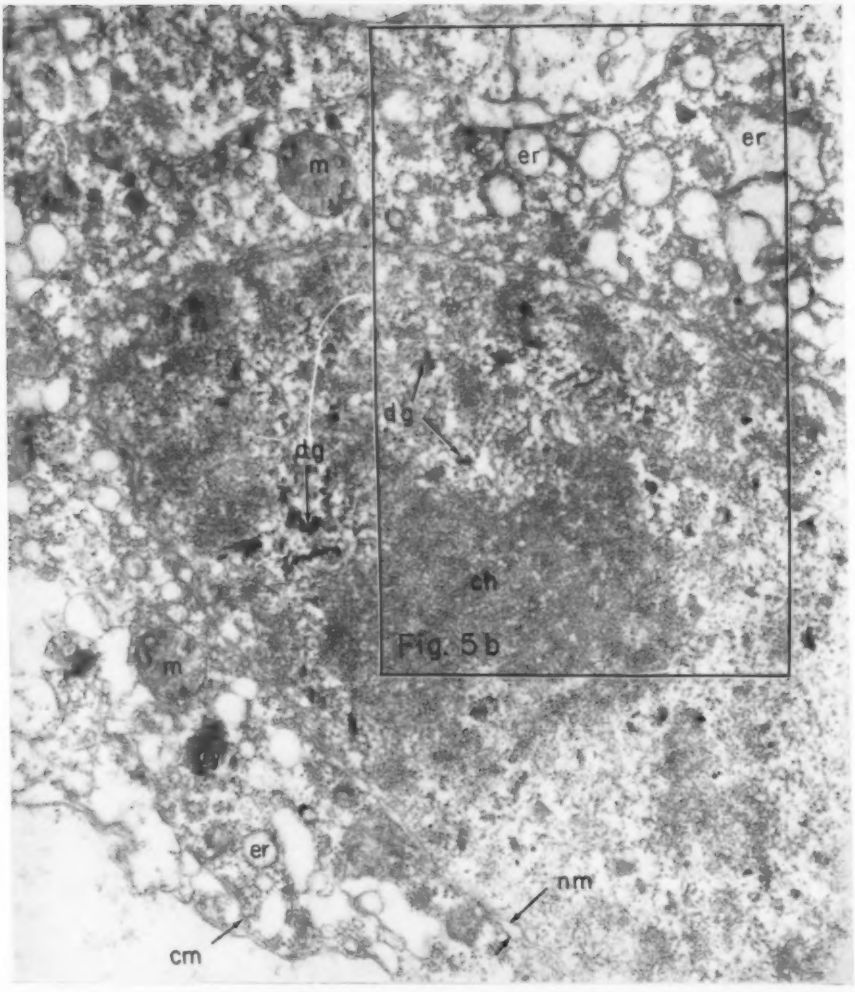


Fig. 5a. Nerve cell which is still intact but which shows definite nuclear and cytoplasmic alterations. dg=dense granules; ch=chromatin; nm=nuclear membranes, which are clearly separated by a space of varying width; m=mitochondrion; cy=cytosome; er=endoplasmic reticulum; cm=cell membrane. × 21,600

posits occurred within these organelles (Fig. 5a). In other cells, the mitochondria were vacuolated and contained moderately osmiophilic granular material (Fig. 7).

In both mild and moderately damaged nerve cells, there appeared well-circumscribed, usually membrane-bound, round or oval bodies of varying size which resembled the structures described in a variety of cell types as "cytosomes," "microbodies," "dense bodies," or "lysosomes."[20] Usually, these structures contained homogeneous, moderately osmiophilic material, although occasionally there were also scattered, dense, irregular deposits (Figs. 5a, 7, and 9b).

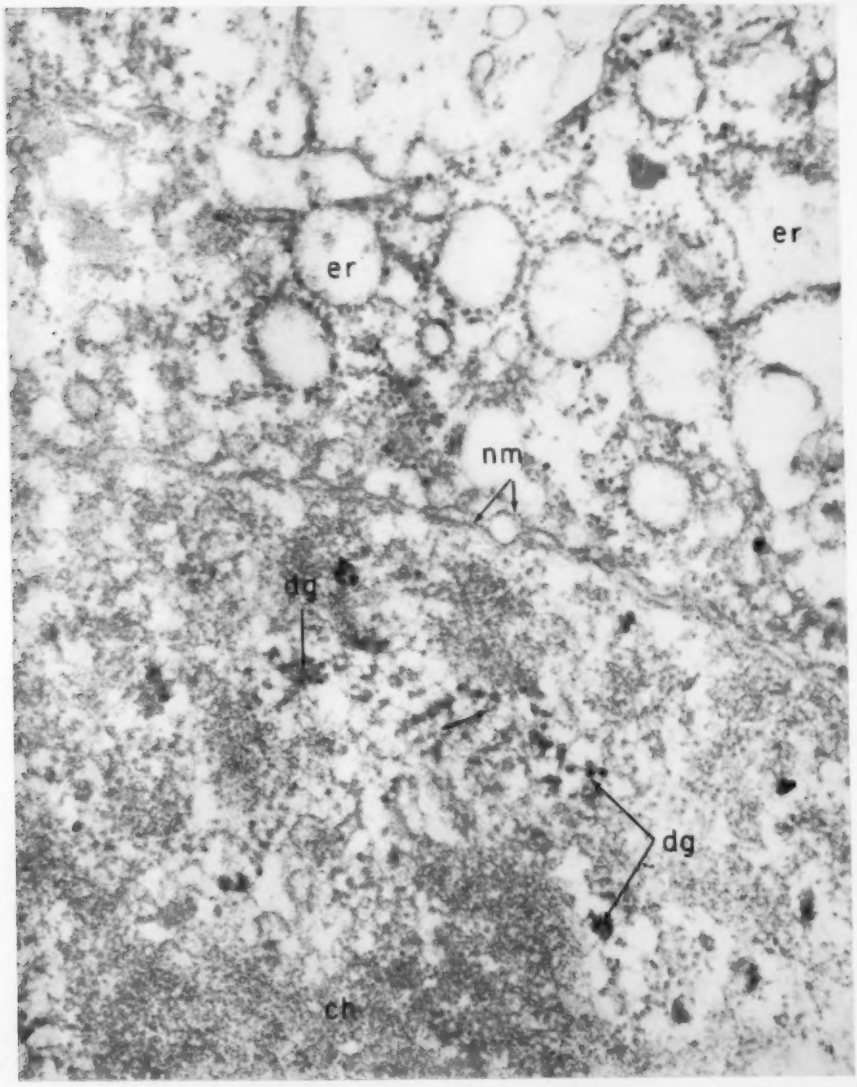


Fig. 5b. Higher magnification of portion of nerve cell outlined in Figure 5a to demonstrate details of nuclear and cytoplasmic abnormalities. Abbreviations are same as used in Figure 5a. Note also small, moderately osmiophilic particles, some of which are attached to membranes of endoplasmic reticulum. × 43,200

In later stages, numerous membrane-bound vacuoles were seen in the cytoplasm, some of which represented swollen mitochondria, while others might be very dilated portions of endoplasmic reticulum (Figs. 6 and 7). Eventually, spaces without limiting membranes

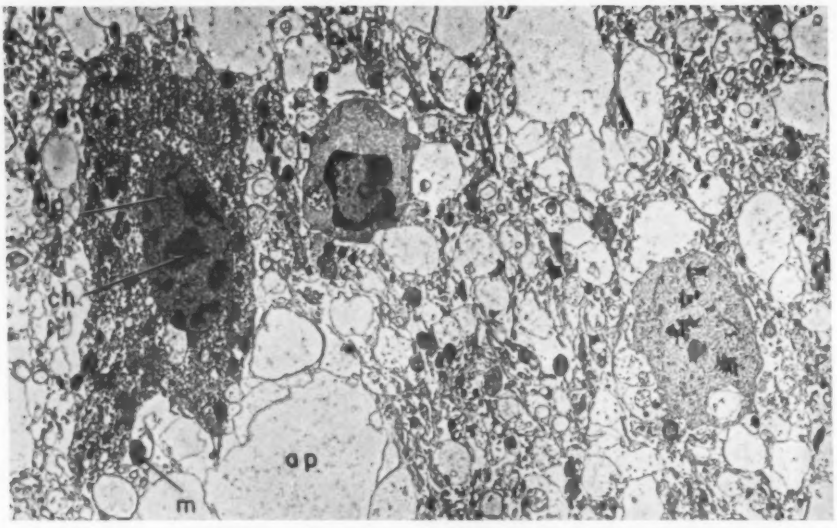


Fig. 6. Severely damaged neuron in area of partial necrosis. To right of medium-sized nerve cell are portions of polymorphonuclear leukocytes, one of which is cut through its nucleus and both of which contain intracytoplasmic inclusions. dg=dense granules; ch=chromatin; m=mitochondrion; ap=swollen and disrupted astrocytic processes. × 4,500

were seen, and, as the cytoplasm became progressively more disrupted, there was loss of the cell membrane and dispersal of organelles into the surrounding necrotic region.

In 2 cells from different animals, both of which showed the usual severe paralysis and were sacrificed on the third day, somewhat more specific alterations were seen; 1 of these cells contained small round particles, a few of which were scattered in the cytoplasm, while others were arranged in an ordered lattice or crystalline pattern (Fig. 9a through c). Some of the crystals were embedded in the ground cytoplasm, and others had only a suggestive and probably fortuitous relation to larger bodies which seemed partially membrane-bound. The individual dense particles were not contiguous but were separated by a relatively electron-translucent region. In addition, the particles themselves showed some variation in density and, in a few instances, seemed to have an electron-translucent central core. The distance between the centers of the dense particulate structures measured approximately 22 to 24 mμ. While it was occasionally difficult to distinguish between reactive microglia and small neurons in this region of the mouse brain, it was believed that this cell was a neuron.

Another example of crystal formation by these particles was seen in a complex formed by a microglia, a polymorphonuclear leukocyte, and a degenerating nerve cell (Fig. 10a and b). The exact location of the crystal could not be ascertained, since the cytoplasmic membranes of the different cells were not clearly separable. Again, no definite relationship to cytoplasmic organelles could be established.

In addition to these crystalline aggregations in small cells, there occasionally occurred highly suggestive, though less definitely crystalline, aggregations of small particles in the cytoplasm of cells which could be positively identified as medium-sized neurons (Fig. 11a and b).

DISCUSSION

The virus assays of homogenates made from brain pools of animals infected one, two, and three days before sacrifice can be correlated with the histologic data. Thus, the virus concentration was very low on the first day when

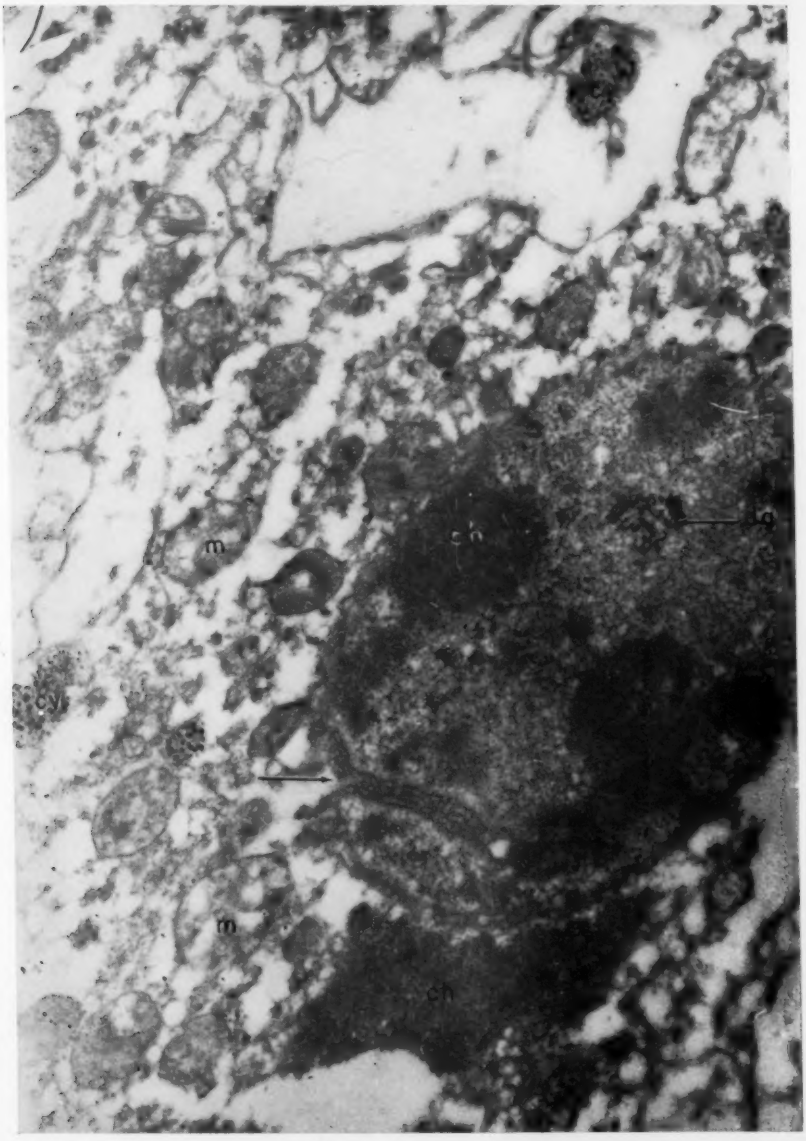


Fig. 7. Necrobiotic nerve cell. There is disruption of cytoplasmic membrane which is out of field, as well as of nuclear membranes which also show deep infolding (arrow). Clumped chromatin (ch) is seen both within and without nucleus. m=mitochondrion; dg=dense granules; cy=cytosome. Numerous vacuoles and empty spaces in cytoplasm cannot be identified. Well-defined endoplasmic reticulum is no longer seen. × 21,600

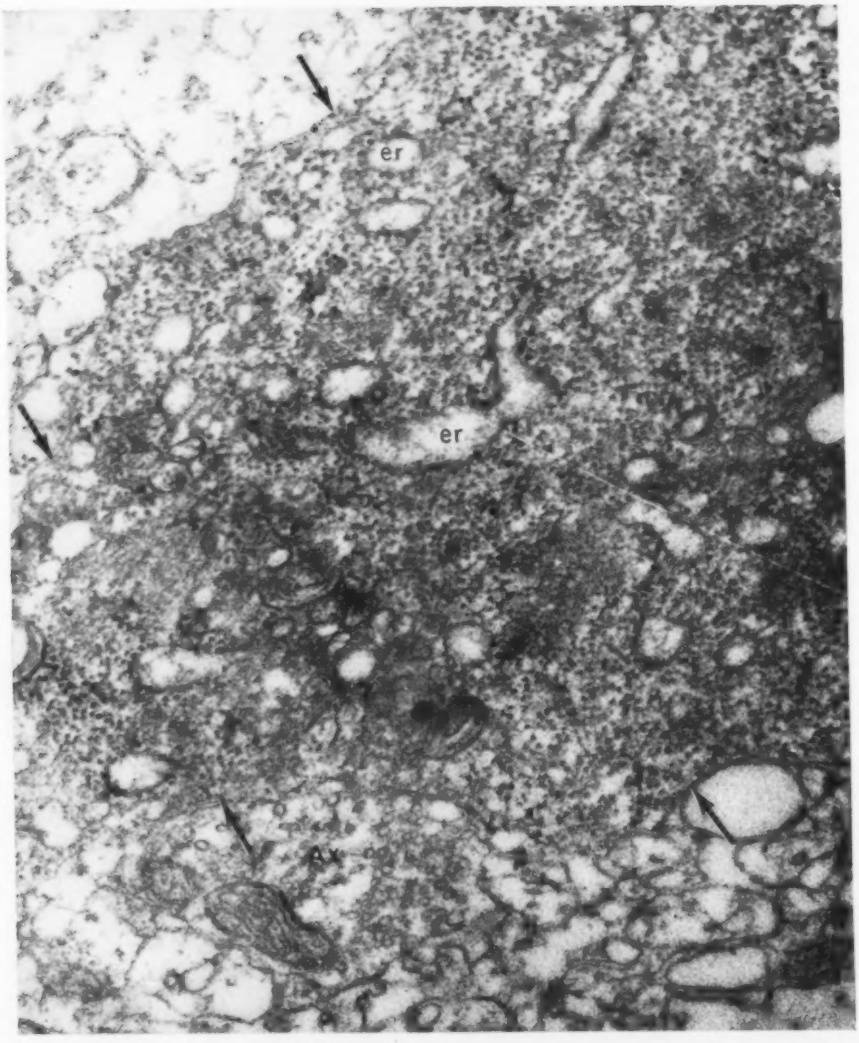
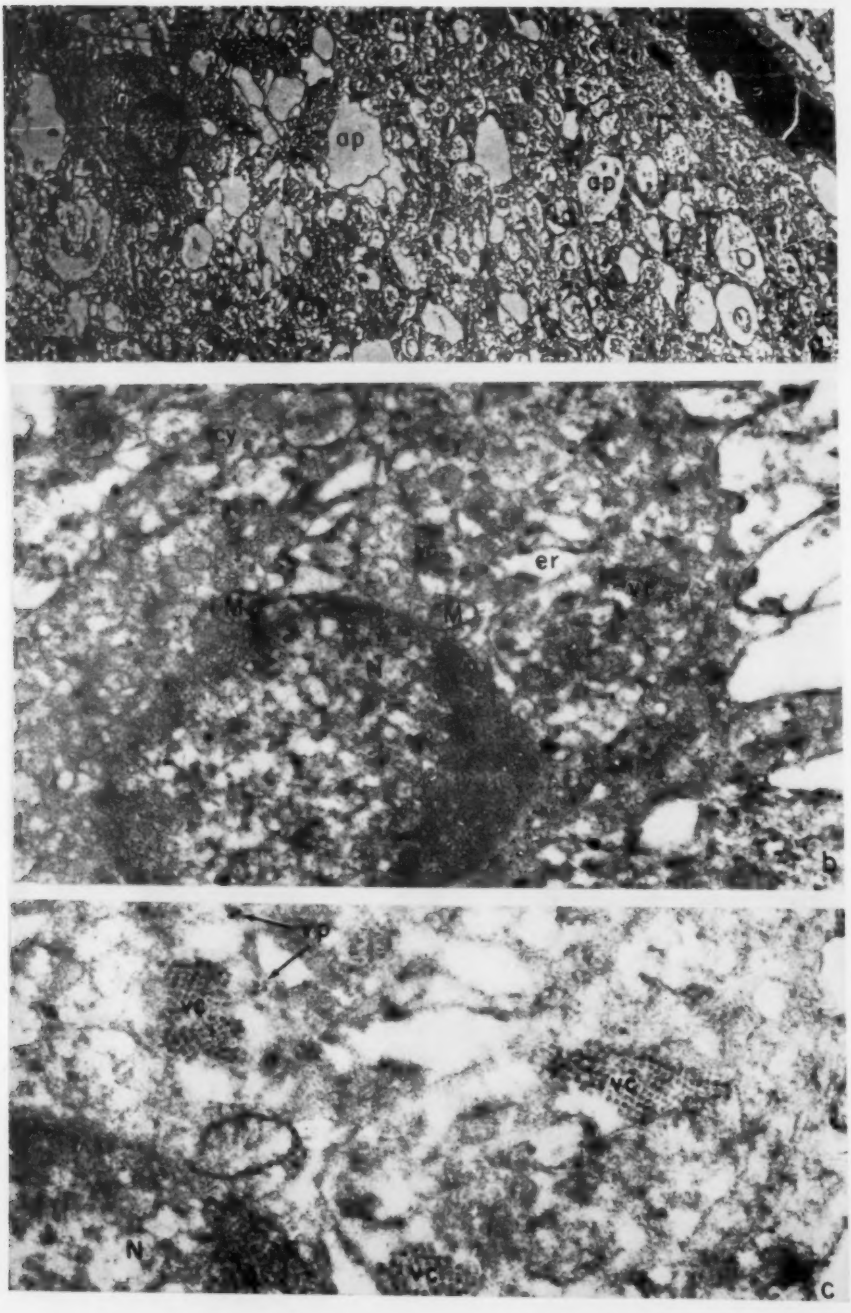


Fig. 8. Dendrite of medium-sized nerve cell which was surrounded by polymorphonuclear leukocytes. Arrows indicate dendritic margins. Note large numbers of small, rather uniform dense particles. Ax=axon containing mitochondria and synaptic vesicles; er=endoplasmic reticulum. × 43,200

Fig. 9, on opposite page, [a] A small cell, probably a neuron, near area of inflammation. N=neuron; ap=astrocyte processes; e=erythrocyte in capillary. × 4,500. [b and c] Higher magnification from area outlined in Figure 9a to demonstrate virus crystals. N=nucleus; M=mitochondrion; er=endoplasmic reticulum; cy=cytosome; vc=virus crystal; vp=virus particle. × 21,600; × 43,200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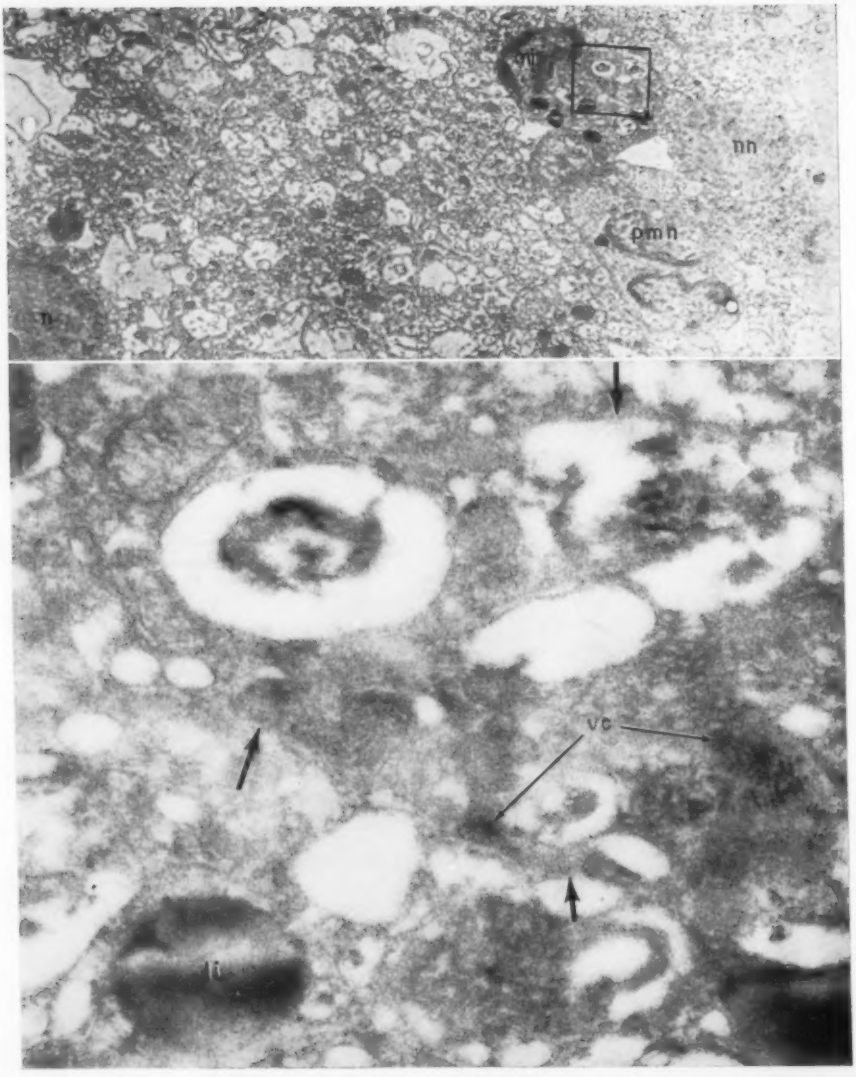

Fig. 10. [a, top] Poorly defined cellular complex formed by necrobiotic neuron whose nucleus can still be recognized (nn), polymorphonuclear leukocyte (pmn), and reactive microglia (mi). In spite of abnormalities in this and neighboring neurons (n), neuropil appears essentially unchanged. × 4,500. [b, bottom] Higher magnification of area outlined in Figure 10a. Cell membranes of adjacent cells cannot be clearly identified, though it is believed probable that region indicated by arrows is nerve cell cytoplasm. vc=virus crystals; li=lipid-containing inclusions in microglia cytoplasm. × 43,200

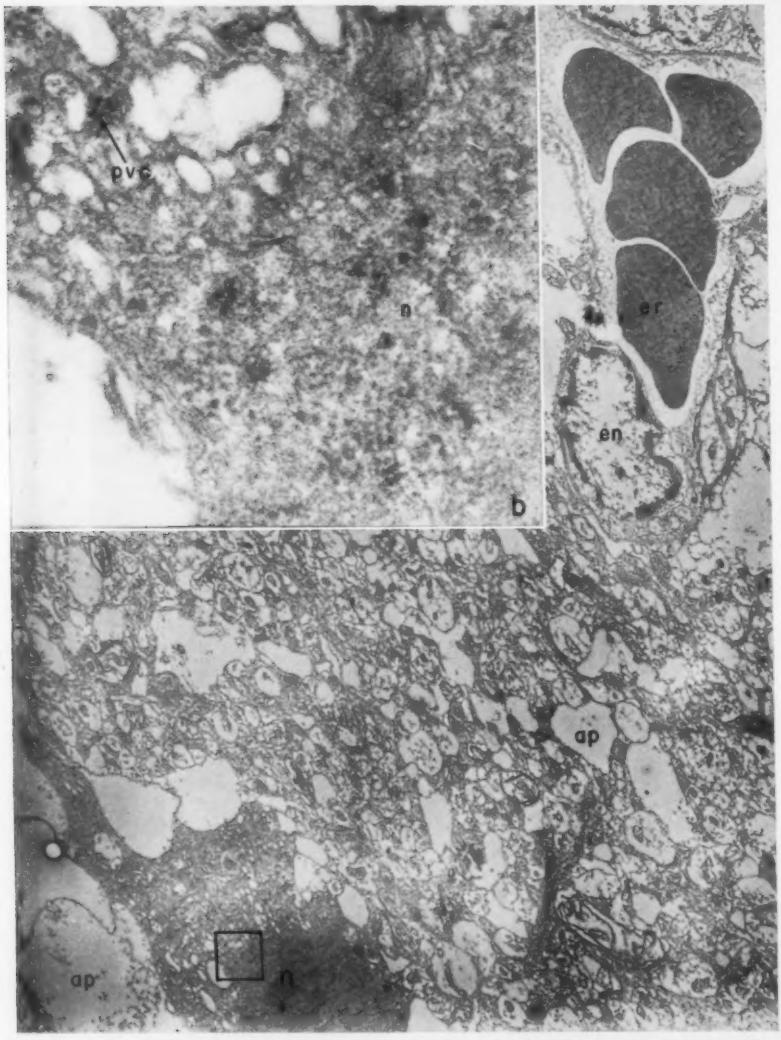

Fig. 11. [a] Medium-sized nerve cell in area of somewhat edematous neuropil. Note relative size of neuron, endothelial cell, and erythrocytes in a capillary. n=nerve cell nucleus; ap=astrocyte process; en=endothelial cell nucleus; er=intracapillary erythrocyte. × 4,500. [b, insert] Higher magnification of area of nerve cell outlined in Figure 11a. n=nucleus containing poorly defined but abnormal granular material; pvc=possible virus crystal. × 43,200

both light and electron microscopic alterations were not apparent. With the marked elevation of virus titer on the second and third days, there was an extensive polioencephalitis. Further consideration of the significance of these findings and their relationship to clinical and biochemical data will be published in a separate communication.[24]

The symptomatology of the animals studied in these experiments and the distribution and character of lesions as demonstrated by light microscopy are very similar to those previously reported after infection by other members of the Columbia-SK group of viruses.[22] The considerable morphologic and virologic evidence supporting our belief that the small particles occurring as intracytoplasmic crystalline aggregations are indeed virus, and are specifically the virus of the MM strain with which the animals were infected, has been previously summarized.[30]

The finding of an intracellular crystalline pattern made up of virus particles would seem to be of some practical and theoretic interest since, in these experiments, sections from the brains of infected animals were studied, rather than cells from infected tissue cultures. The latter are strongly adapted cells in a foreign environment[18–20] rather than a part of tissue which a few days before was in a normal physiologic state. Therefore, the similarity between at least some aspects of virus growth (that is, crystal formation) under true in vivo conditions and the tissue culture findings of numerous other workers[31–36] would seem to indicate an analogous biologic process occurring in the 2 systems.

In spite of differences in experimental method, certain similarities with previous investigations on virus-infected cells can be noted. Thus, Morgan and associates,[33] studying the development of herpes simplex in HeLa cells, described 2 different intranuclear granular components, 1 of which closely resembles the deeply osmiophilic granules in our experiments. These investigators remarked on the absence of such structures in control material, and we also have not seem them either in normal neurons or nerve cells rendered necrobiotic by trauma or radiation.[37] This suggests that the dense granules may represent a special reaction of the nucleus to virus infection, possibly a degenerative change caused by virus infection or a by-product of virus formation. The second abnormal granular component in the nuclei of HeLa cells infected with herpes simplex could be clearly distinguished from the reticular or more finely granular chromatin and was convincingly shown to be intimately associated with virus production. The relation of this component to structures seen in our material is less certain. While some of the nuclei in our experiments show a granular component that is certainly different from the densely osmiophilic granules, it cannot be so easily separated from chromatin (Fig. 7), and, furthermore, definite intranuclear virus particles have so far not been identified by us.

Ruska, Stuart, and Winsser,[38] studying polio-infected kidney epithelium, described a perinucleolar accumulation of "virus-like" particles which bear a resemblance to the granular structures seen in some of the altered nuclei in our material. Lepine, Croissant, and Wyckoff[39] have reported the occurrence of globular bodies in the nuclei of nerve cells of mice infected with mouse-adapted poliovirus; however, similar structures were also seen in their control preparations, and the technic of tissue preparation used by these investigators differs so greatly from ours that it is not fruitful to compare electron micrographs.

The significance of the widened space between inner and outer nuclear membranes in relatively intact neurons is uncertain. This space is considered to be a component of the endoplasmic reticulum [40,41] which is also of increased prominence and seems to be appreciably, though less strikingly, widened in many of the severely damaged neurons. One can speculate that such a change could be associated with a shift of fluid from the nucleus to cytoplasm and might thus be an early stage in the production of the pyknotic nucleus of the necrotic neuron.

Parallel with the nuclear changes is the apparent increase in number and change in pattern of distribution of small particles in the cytoplasm. At the resolutions employed in these experiments, no clear-cut morphologic distinction could be made between these excessively numerous and abnormally arranged particles and the normal ribonucleoprotein granules which constitute the main basophilic component of the Nissl bodies of light microscopy.[42] It is somewhat unlikely that this cytoplasmic alteration is simply a degenerative phenomenon, since similar changes were not seen in neurons injured by mechanical trauma or x-radiation;[37] however, it must be admitted that the most prominent neuronal alteration seen in these infected animals with the light

microscope was "ischemic" degeneration, a type of change not usually seen with trauma or x-radiation. More experience with the ultrastructure of various kinds of nerve cell damage must be gained before one can be reasonably certain that any given alteration is specific.

It is conceivable that these particles reflect a nonspecific attempt on the part of the damaged cell to reconstitute normal organelles. This finding could then be considered the electron microscopic equivalent of the reformation of Nissl substance that is known to occur in injured but recovering cells following poliovirus infection.[3]

Another possibility is that these particles represent virus or virus precursors. There is some evidence that the small, spheric animal viruses have a ribonucleic acid core[13] surrounded by a protein shell,[12,13,43,44] and Crick[45] has noted theoretic similarities between the structure and composition of these viruses and ribonucleoprotein or "microsomal" particles. It would not be surprising if their electron microscopic appearance was very similar.

Some of our findings can be interpreted in terms of modern concepts of virus multiplication. It has generally been believed from light microscopic work[2] that the earliest pathologic changes due to poliovirus occur in the cytoplasm and that virus multiplication also takes place here. In addition, the fluorescent antibody studies of Buckley[46] indicated the presence of poliovirus antigen at an early stage of infection within the cytoplasm, at a time when no cellular pathology was evident and before fluorescence was seen in the nucleus. With fractionation technic, active virus has been detected first in the cytoplasm and only later in the nuclear fraction.[47] On the other hand, utilizing ultraviolet microspectrophotometry in a study of nervous tissue from polio-infected human beings and animals, Caspersson[7] and Hydén[6] concluded that, in the relatively early stages, the nucleolus and nucleolus-associated chromatin were actively synthesizing ribonucleoprotein and that this synthesis reflected intranuclear virus production.

It now seems probable that, at least for some of the animal viruses, synthesis of the antigenic protein portion of the particle and the ribonucleoprotein portion occur at different sites,[32,48] and, on such a basis, with assembly of the mature and infective virus in the cytoplasm, findings of different investigators can be reconciled. Our findings, though by no means conclusive, could support such a "two-stage" hypothesis. Thus, the relatively early nuclear alterations could reflect synthesis of the ribonucleoprotein portion of the virus, which would, of course, not be antigenically active and so would not be visible by the fluorescent antibody technic. Eventual combination of this constituent with the protein shell could then occur within the cytoplasm, would be antigenically active, and might be morphologically similar to ribonucleoprotein particles.

The presence of cytosomes has been reported in both normal and abnormal cells of various kinds, and there is some evidence that they tend to accumulate in response to injury or irritation.[49] While not common or numerous in normal neurons, they have also been noted to occur here after metabolic or traumatic irritation[50,51] and, like the mitochondrial abnormalities, cannot be considered in any way a specific response to viral infection.

It is apparent that there is yet much to be learned about the significance and method of production of the cellular alterations in virus infection. Further investigations using high-resolution electron microscopy may help to elucidate the site and manner of replication and maturation of the infectious particle and clarify its role in the production of nerve cell necrosis.

SUMMARY

Mice were inoculated subcutaneously with approximately 0.1 cc. of a 10^{-4} dilution of a brain homogenate infected with Columbia-SK virus (MM strain), resulting in severe paralysis on the second and third day after infection. Animals were sacrificed at twenty-four, forty-eight, and seventy-two hours after infection, and portions of the brain were utilized for light and electron microscopic study as well as for virologic determinations. Low concentrations of virus were noted in homogenates of brains from animals sacrificed one day after infection, while a progressively high titer of virus was found in the second- and third-day groups.

With the light microscope, the lesions were

seen to be concentrated in the prepyriform cortex and consisted of a severe necrotizing polioencephalitis. The heavy polymorphonuclear infiltrate often obscured the necrobiotic neurons.

Electron microscopy of such areas showed details of both nuclear and cytoplasmic involvement. In the nucleus, there occurred very dense, irregular granules, clumping of the chromatin, and a less dense and more regular granular component which could not be clearly separated from the chromatin. Marked widening of the perinuclear space was also observed. Within the cytoplasm, there occurred a crystalline aggregate made up of small particles which, on the basis of morphologic and virologic evidence, are believed to represent virus. In addition, in some relatively intact neurons, there seemed to be an increase in number and change in distribution of a small particulate component of the cytoplasm. Mitochondrial alterations and cytosomes were also noted.

The possible significance of some of these observations with regard to concepts of virus multiplication and virus-host relationships was briefly discussed.

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Hemangiopericytoma of the meninges (angioblastic meningioma of Cushing and Eisenhardt)

Clinicopathologic aspects and follow-up studies in 8 cases

Maj. Francis Kruse, Jr., U.S.A.F., M.C.

STOUT AND MURRAY[1] described in 1942 a type of neoplasm believed to be derived from the capillary pericyte, a cell first described by Rouget[2] in 1873 and studied in the frog by Zimmermann[3] in 1923. Naming this tumor "hemangiopericytoma," Stout and Murray stated that it is characterized by endothelial sprouts surrounded by a sheath of rounded and sometimes elongated cells. These cells, which comprised the bulk of the tumor, were regarded as pericytes, that is, cells with long processes wrapped about capillaries which were presumed to be contractile and to serve as modified smooth muscle capable of altering the size of the lumina. This initial report dealt with tumors of this kind in 8 human cases. A subsequent paper by Stout[4] added 24 cases in which the tumor was variously situated, and included in the report was a description of a hemangiopericytoma in a dog. Since then, many more of these tumors have been documented, and there have been 2 extensive reports of hemangiopericytoma in the dog.[5,6] In man, they have been located most commonly in soft tissues, particularly in the thigh and buttock, but some have been found in retroperitoneal[7] and omental[8] tissues, sigmoid colon,[9] uterus,[10] orbit,[11] axilla,[12] and meninges. In an analysis of hemangiopericytomas occurring in 32 children and preadolescents—from a few months to 16 years of age—Kauffman and Stout[13] found that only 1 of the tumors was located intracranially.

Begg and Garret[14] were the first to describe a tumor in the meninges which they referred to as "hemangiopericytoma," and Fisher, Davis, and Lemmen[15] were the second. In a more recent publication on hemangiopericytomas, Stout[16] listed 4 more meningeal tumors of this kind. These tumors were included by Bailey, Cushing, and Eisenhardt[17] and by Cushing and Eisenhardt[18] in the category of "angioblastic meningioma" (Cushing and Eisenhardt, type IV, variety 1). In a review of 263 meningeal tumors, Simpson[19] noted that 5 corresponded morphologically to hemangiopericytoma, but he called them "undifferentiated sarcoma."

In the course of an evaluation of some 900 cases of tumor of the meninges from the files of the Armed Forces Institute of Pathology, there were 8 in which the tumor had the characteristics of hemangiopericytoma. These form the basis of the present report. The locations of the tumors were no different from those of other types of meningioma, but 3 of the 8 were peritorcular.

CLINICAL FEATURES

Of the 8 patients, 6 were men and 2, women. At the time of initial operation, the patients' ages ranged from 19 to 66 years—the second decade of life in 1, third decade in 3, fifth in 2, and sixth and seventh in 1 each (see table).

Headache was the most common symptom, occurring in 5 of the patients. Jacksonian sei-

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CLINICAL ASPECTS AND SITES OF ORIGIN IN 8 CASES OF MENINGEAL HEMANGIOPERICYTOMA

Case no. and AFIP no.	*Age and sex*	*Nature and duration of symptoms and signs*	*Location of tumor*	*Course and current status*
1 764351	66 F	Headache, paresis, and jacksonian seizures of right leg, 4 months' duration. Slight paresis of right arm	Left frontoparietal, parasagittal	Living 4 years after initial operation. Reoperated 3 years afterward, with radical tumor removal
2 630741	19 M	Headache and episodes of vertigo, nausea, and vomiting 2 months before admission	Right posterior fossa, arising from tentorium	Living 7 years after initial operation. X-ray therapy given. Reoperated 6 years after initial operation, with apparent complete removal of tumor
3 284181	44 M	Paresis and paresthesias of left leg for 5 months. Single seizure on day of admission; origin in left arm	Right frontoparietal	Living 12 years after initial operation. Reoperated 9½ years after initial surgical intervention, but tumor recurrence now evident at site of operative defect
4 831989	22 M	Suboccipital headache for 8 months. Ataxia, vertigo, lethargy, nausea, and vomiting for 2 months. Jacksonian seizures in left leg on 2 occasions	Left posterior parietal, parasagittal	Died 1 year, 4 months after initial operation. No autopsy was done, but death was thought to be due to basilar artery thrombosis
5 838917	43 M	Headache, diffuse, severe, at 4 months	Left posterior fossa, arising from tentorium	Died 2½ years after initial operation. X-ray therapy given postoperatively. Reoperated 2 years later with removal of small amount of tumor
6 212847	53 M	Paresthesias and paresis of left leg and arm for 2 months and 2 weeks, respectively. Slight paresis in other extremities	Intraspinal at levels C_2 and C_3	Died 4 years after initial operation. X-ray therapy was given subsequent to removal. Reoperated 3 years after the first surgical intervention; tumor compressing cervical roots was removed
7 856743	28 M	Occipital headache at 4 months. Nausea and vomiting and visual loss (left homonymous hemianopsia)	Right occipital, medial, attached to falx	Died 5 years after initial surgical intervention and 2 months after reoperation. X-ray therapy postoperatively.
8 163532	22 F	Jacksonian seizures on left side, primarily of face, with residual facial paresis, 1 day before admission to hospital	Right frontal, parasagittal	Died 13 years after initial surgical intervention. No apparent intracranial recurrence, but metastasis to vertebra 8 years and 2 metastases to femur 11 years postoperatively

zures were observed in 4. The clinical disturbances, in no way different from those observed in other meningiomas in similar locations, appeared from within twenty-four hours to eight months before surgical intervention.

In nearly all of the cases, the tumor was extremely vascular, making the operative procedure difficult and necessitating blood transfusion.

Laboratory studies provided no specific diagnostic aid. The cerebrospinal fluid in some of the patients showed increased protein and/or elevation of pressure. Plain films of the skull disclosed evidence of the tumor in 2 of the cases. Diagnostic air studies and arteriography were helpful in localization, as was the electroencephalogram in the cases in which the tumor was supratentorial. A tracer study with Cu^{64} provided exact localization in the 1 case in which it was employed (Case 4).

Follow-up study disclosed local tumor recurrence in 6 of the 8 cases and lack of clinical evidence thereof in the other 2 (Cases 4 and 8). Death occurred after tumor recurrence in 5 of the cases (Cases 4 through 8). Metastasis to distant sites occurred in 1 (Case 8). Reports of 4 of the cases are provided to illustrate facets of the clinical course.

CASE REPORTS

Case 2. A 19-year-old white man was admitted to hospital in November 1953 complaining of dizziness, nausea, vomiting, and headaches, all of about eight months' duration. During several weeks immediately before hospitalization, the headaches became severe, particularly in the right frontotemporal region. Vertigo was so advanced that he was forced to stay in bed. Physical examination revealed papilledema, nystagmus on gaze to the left, and a perceptive type of hearing loss in the right ear. Deep muscle reflexes were slightly increased on the left. The plantar response was downward.

Routine laboratory studies showed nothing remarkable. Plain films revealed a normal skull. A ventriculogram showed that the lateral and third ventricles were in their normal positions but were slightly dilated. The fourth ventricle was not visualized. Suboccipital craniectomy was performed. A meningioma attached to the tentorium cerebelli and compressing the right cerebellar hemisphere was partially excised. Profuse hemorrhage necessitated transfusion of 3,000 cc. of blood during the procedure.

After convalescence, the tumor region was exposed to x-ray therapy. During the next four years, the patient felt well except for residual symptoms of cerebellar dysfunction.

In September 1959, right homonymous hemianopsia was noted. Craniotomy was again performed, and a 5 × 6 cm. tumor attached to the tentorium and extending toward the midline was removed, apparently in its entirety.

Case 3. A 44-year-old white man was admitted to hospital in February 1948 with the complaint of clumsiness and weakness of the left foot. He had first noticed a tendency to stub his toe on curbs and stairs, and, about five months before admission, an intermittent sensation of "pins sticking" appeared in the left foot. The weakness in his left foot and leg had been ingravescent until he was unable to dorsiflex the foot and occasionally could not support his weight on his left leg. On the day of admission, sudden "jerking" occurred in the left arm and consciousness was lost; "jerking" was then observed throughout the left extremities, and then the patient became cyanotic and bit his tongue. Physical examination after he regained consciousness revealed a "slapping gait" and left hemiparesis. The deep muscle reflexes in the left arm and leg were increased, but the plantar response was downward. The cranial nerves were intact. Laboratory studies were not remarkable except that the cerebrospinal fluid had an initial pressure of 290 mm. H_2O and total protein of 75 mg. per cent and was globulin-positive. Skull films showed enlarged and tortuous vascular channels in the right frontal and parietal regions.

Craniotomy revealed a large meningioma of the right frontoparietal area. Extreme vascularity of the tumor made removal difficult. Subtotal removal was accomplished. During the course of the operation, the patient was transfused with 4,000 cc. of whole blood. He had residual left hemiparesis but at the time of discharge was able to walk with the aid of a cane.

The patient returned to hospital in September 1957, after four months of severe, constant aching over the right side of his head. On examination, the previous operation site was found swollen, tense, and tender, and a loud bruit was heard on auscultation of this area. Part of the parietal bone was removed along with 100 gm. of tumor. Bleeding was difficult to control. Removal of the tumor was again incomplete.

The patient became ambulatory after the reexploration. When last examined in July 1959, he was bedfast, and a large tumor mass could be palpated at the site of the skull defect.

Case 6. A 53-year-old white man was admitted to hospital in September 1947 complaining chiefly of weakness of the left side of his body. For two months before admission, he had noted a "pins and needles" sensation and progressive weakness in his left leg. Two weeks before admission, similar disturbances occurred in the left arm and there was some reduction in motor power in the right arm and leg. Physical examination revealed weakness of the left extremities, particularly marked in the leg. Deep muscle reflexes were increased on the left. There were no sensory deficits. A spinal tap revealed partial subarachnoid block. After a myelogram, which disclosed a filling defect at the level of the second and third cervical vertebrae, laminectomy revealed a well-encapsulated intradural-extraspinal tumor compressing the cord. The tumor had the gross appearance of a meningioma and was removed piecemeal. The operative procedure was complicated by marked hemorrhage from the tumor, and removal was obviously incomplete. Recovery was uncomplicated and there was complete relief from symptoms. Because of the presence of numerous mitotic figures, the region of the tumor was given x-ray therapy.

Two years after the initial operation, the patient began to complain of recurrent sharp pain in the left side of his neck. At a second operation in October 1950, the recurrent tumor, which compressed the third cervical root, was removed and the root severed. The patient died from bronchopneumonia in December 1951. No autopsy was performed.

Case 8. A 22-year-old white woman was admitted to hospital in October 1945, one day after a seizure in which she noted twitching of the left side of her face, difficulty in speaking, and momentary loss of consciousness. After the initial episode, attacks occurred at intervals of approximately fifteen minutes but without loss of consciousness. During an attack, it was noted that "the left-sided facial twitching involved most of the muscles of the face and neck on the left, blinking of eyes, contractions of jaw muscles; left side of face drawn in spasms to the left; patient unable to talk during attack but understands and obeys what is said to her; also has difficulty controlling muscles of left arm during attack." Physical examination revealed left facial weakness and blurring of the margins of both optic disks. An electroencephalogram was interpreted as showing diffuse cerebral dysrhythmia with focalization in the right frontotemporal region. Roentgenograms of the skull revealed an area of diminished density in the right anterior parietal region, the defect involving only the inner table. After a ventriculogram, which showed displacement of the ventricular system, indicative of a right frontoparietal lesion, right frontoparietal

craniotomy was performed. A large meningioma together with the involved dura and bone was removed. It proved to be a hemangiopericytoma. The postoperative course was uneventful.

Some eight years later, after the onset of back pain, a mass was found in the body of a lumbar vertebra. It was excised apparently in its entirety. The tumor was identical with that removed from the intracranial cavity. Eleven years after the original operation, a lesion was noted in the left femur. After biopsy, which also showed the features of hemangiopericytoma, a midthigh amputation was performed. The patient died in the winter of 1958, thirteen years after the first operation. Autopsy was not carried out.

PATHOLOGIC FEATURES

The gross appearance of the meningeal hemangiopericytomas is somewhat varied, but all have been solitary and apparently well encapsulated. They may be spheroidal or occasionally lobulated, as in our Case 8 (Fig.1), and usually have seemed to the surgeon to have the gross appearance of meningothelial or fibroblastic meningioma. In the course of removal, most of these tumors were noted to be extremely vascular, and extirpation was complicated by excessive loss of blood. No gross extension into central nervous system tissue was noted, and in all cases the tumor was grossly well encapsulated. In Case 1, tumor invasion of the longitudinal sinus was noted at the time of operation. After fixation, all the tumors were firm and the color of their cut surfaces was white to tan. Small areas of necrosis and small hemorrhages were noted in some of the tumors.

Fig. 1. *(Case 8)* Frontoparietal portion of skull with meningeal tumor. Note lobulated character and well-encapsulated appearance. Courtesy of Armed Forces Institute of Pathology. Neg. 163532-2

On microscopic examination, the tumors were found composed of cells with small, relatively uniform, oval or elongated nuclei having moderate amounts of reticulated chromatin. The cytoplasm was, as a rule, sparse, and the cells tended to have a spindle appearance and were arranged in suggestive whorls or pinwheels. Mitotic figures, present in varying numbers, were observed in all the cases. Throughout the tumors, there was an abundance of thin-walled vascular channels lined by a single layer of endothelial cells (Fig. 2). These channels were sometimes collapsed and thus not obvious (Fig. 3), but Wilder and Gomori silver preparations revealed them clearly (Fig. 2B and D). The reticulum pattern distinguished the tumor from other neoplasms in that the tumor cells lay external to the vascular endothelium rather than within reticulum rings, as in hemangioblastoma. Frozen sections stained with oil red O or Sudan IV showed no intracellular lipid, and phosphotungstic acid-hematoxylin preparations revealed no demonstrable fibrils.

In 1 patient (Case 5), tumor biopsies were examined before x-ray therapy and two years afterward. No morphologic differences in the 2 specimens were seen. In the 1 case in which metastasis occurred (Case 8), the tumor contained foci of cartilaginous and osteoid tissue (Fig. 4). The primary tumor in this case permeated the skull between bony trabeculae in the same manner as in other types of meningioma. The possibility of extension of the tumor into the central nervous system tissue could not be evaluated because of lack of adequate autopsy material.

DISCUSSION

Symptoms of intracranial origin in the present series appeared in a range of two days to eight months before surgical intervention. In a series of 121 meningiomas, Lapresle, Netsky, and Zimmerman[20] noted that the duration of symptoms before operation was less than two years in only 43%. Of the 8 tumors in our se-

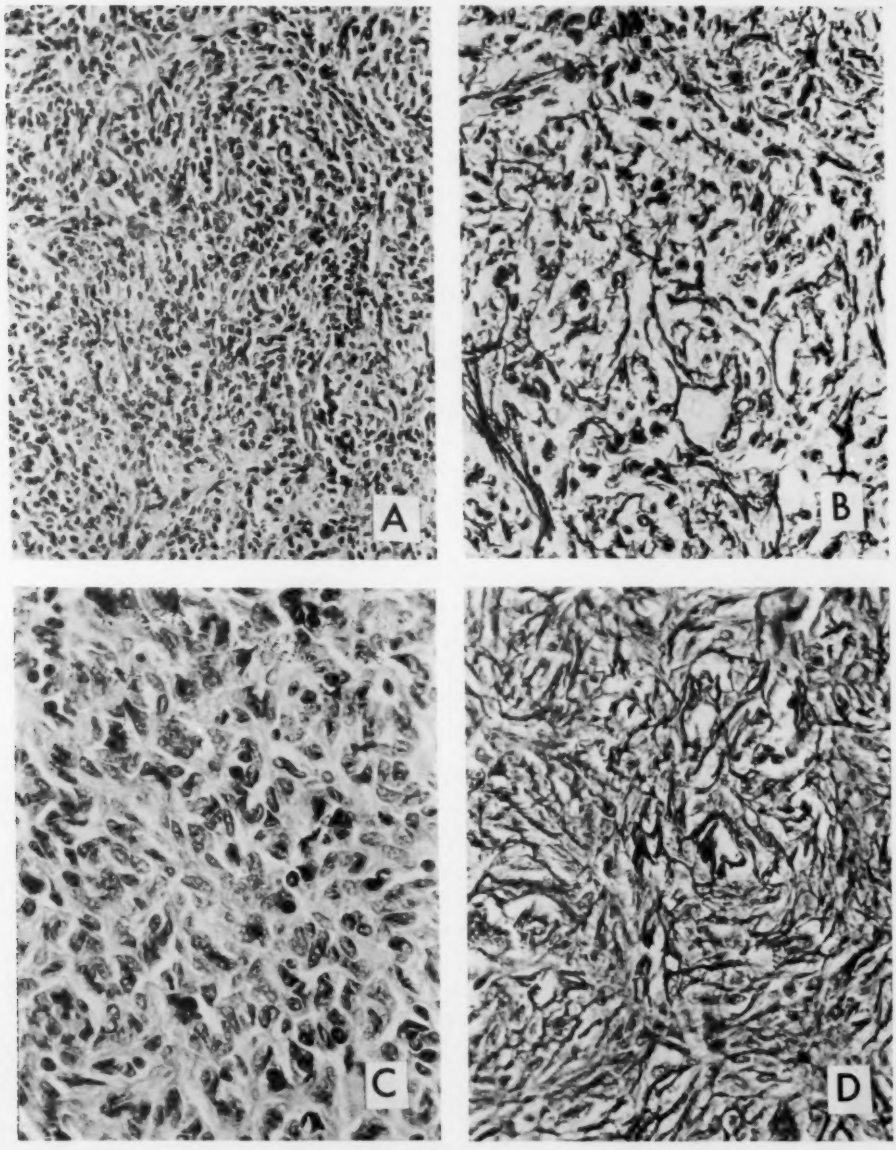

Fig. 2. (A and B, *Case 5;* C and D, *Case 7)* Typical examples of meningeal hemangiopericytoma. Note oval to elongated, relatively uniform tumor cells and scattered tiny vessels. Reticulum fibers are about individual cells and groups of cells. A, × 150; B, C, and D, × 400. A and C, hematoxylin-eosin stain. B, Gomori silver reticulum stain. D, Wilder reticulum stain. A, AFIP Neg. 59-6623; B, 59-6624; C, 59-6932; D, 59-6933

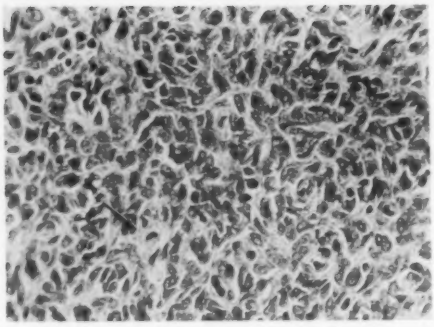

Fig. 3. *(Case 6)* Intraspinal hemangiopericytoma. Pattern is practically the same as in Figure 2. Mitotic figure at lower left (arrow). × 400. Hematoxylin-eosin stain. AFIP Neg. 59-6633

ries, 6 recurred between one and one-half and nine and one-half years after initial surgical removal.

Type of clinical disturbance and laboratory and radiologic data were of no value in diagnosis of this particular type of meningeal tumor. However, peritorcular site may have some significance, as 3 of the 8 tumors in the present series were in that location, as were also 5 of the 6 "angioblastic meningiomas" (type IV, variety 1) of Cushing and Eisenhardt.[18] The gross appearance was not greatly different from that of other meningeal tumors, although suspicion may be aroused by excessive bleeding during operation. Actually, microscopic examination of the tumor is the only reliable means of identification. Surgical excision has been found the treatment of choice. Although some hemangiopericytomas in our series as well as in the series of others have been subjected to x-radiation, the number of cases is too small to allow conclusions as to its efficacy. Radiation therapy is said to have been of some value postoperatively in cases in which complete surgical excision was not possible.[21]

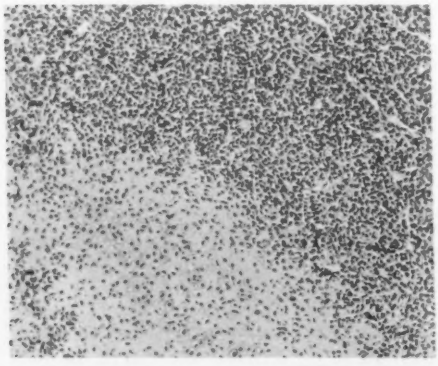

Fig. 4. *(Case 8)* Area from primary meningeal tumor, showing thin-walled vascular channels with endothelial cells strikingly similar to cells composing main bulk of tumor. Note focus of osteoid tissue. × 150. Hematoxylin-eosin stain. AFIP Neg. 59-6608

In the present series, the characteristic cell type, the thin-walled vascular channels, and the extraluminal position of the tumor cells, as described by Stout,[16] were evident in all the tumors. In other ways, too, there was striking morphologic similarity of the neoplasms, the appearance being that which McCormack and Gallivan[22] described as the mature type of hemangiopericytoma. These authors noted cytologic variations ranging in form from smaller cells with oval nuclei and minimal cytoplasm arranged in compact masses to spindle cells with more abundant cytoplasm and a tendency to whorl formation. They also remarked that hemangiopericytoma could thus be graded from immature (small cell) to mature (spindle cell) forms and that the cut surface of the mature form in the fixed specimen was more often tan, although no correlation with clinical behavior could be established.

The interpretation of the characteristic histologic picture as made by Stout[4] is the primary basis for the pericyte theory of oncogenesis, a theory which has gained some support from the tissue culture studies of Murray and Stout[23] and of Fisher, Kaufman, and Mason[24] but not from electron microscopy. In the opinion of the present author, the pericyte cannot be conclusively implicated. The term "hemangiopericytoma" is used in the present paper as a matter of convenience. Being less specific, the appellations "angiosarcoma" and "angioblastic sarcoma" may be more acceptable. In his review of recurrent meningiomas, Simpson[19] has chosen to call this type of tumor an "undifferentiated sarcoma," but this term is inadequate because it does not connote vascular

participation in development of the tumor. Areas resembling hemangiopericytoma have been noted in a variety of malignant mesenchymal neoplasms which otherwise are characteristic fibrosarcomas, synovial sarcomas, or some other tumor.[25] Such observations do not, in the opinion of the author, weaken the concept of hemangiopericytoma as an entity.

The primary tumor in Case 8 is of interest because of the presence in it of foci of osteoid and cartilaginous tissue. The meningeal hemangiopericytoma reported by Fisher, Davis, and Lemmen[15] was grossly and microscopically identical to the tumor in our Case 8 and also contained foci of osteoid tissue and cartilage. Fisher and his associates considered that such foci represent metaplasia or developmental variation; they stated, "A similar phenomenon is well recognized in other primitive mesenchymal neoplasms in which foci of various mesenchymal elements may be encountered." The presence of osteoid and cartilaginous tissue in our tumor should not invalidate its classification as hemangiopericytoma because these types of tissue are found in a variety of meningeal tumors and thus are in no way specific.

When, in cases of hemangiopericytoma, a tumor mass appears after considerable delay at a site distant from the original mass, as in our Case 8, there is the question whether the 2 grew independently or whether metastasis occurred. Delayed metastasis, even in the absence of apparent recurrence at a primary site, it well known and has been demonstrated in a variety of mesenchymal and epithelial neoplasms. The occurrence of delayed metastasis is also not alien to the behavior of hemangiopericytoma when arising in extracranial sites.

SUMMARY

This report deals with 8 cases of hemangiopericytoma of the meninges. The clinical aspects and gross characteristics of these tumors fail to provide significant information as to diagnosis. Identification depends entirely on the histologic pattern, which is diagnostic.

The clinical importance of these 8 tumors lies in their malignant behavior, as indicated by recurrence in 6 and metastasis in 1.

The author wishes to express his appreciation to Dr. Webb Haymaker of the Armed Forces Institute of Pathology.

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Some comments on Wallenberg's lateral medullary syndrome

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and Russell N. DeJong, M.D.

DURING DETERMINATION of the prognosis of certain of the brain stem vascular syndromes,[1] some detail had been gathered concerning that of the posterior inferior cerebellar artery (Wallenberg's[2] retroolivary or lateral medullary syndrome). This unique neurologic entity has attracted the attention of generations of neurologists since the first report of Alexander Marcet[3] in 1813, who described the case of another physician who recounted his own symptoms. The list of those who have written since on this subject is extensive, as revealed in the detailed bibliography given by Louis-Bar.[4] It became evident that, in spite of the many reports of this syndrome in the literature and a few detailed analyses, there was much that was unexplained and of interest. Therefore, a further study of our cases was carried out from the point of view of symptomatology and anatomic localization.

What follows is a detailed analysis of the symptoms in relation to each other and to the presumed location of the infarct. The ideas presented are gained strictly from clinical analysis and anatomic reasoning; no pathologic correlation was available for the present group of cases.

Of the original 75 patients with syndromes of the superior, anterior inferior, and posterior inferior cerebellar arteries, the 2 with involvement of the anterior inferior cerebellar artery were automatically excluded. In addition, close analysis of the cases classified previously[1] as syndromes of the superior cerebellar artery disclosed that it would be more logical to consider these as atypical examples of the lateral medullary syndrome. Of the total of 62 cases of retroolivary syndrome and 11 that were previously attributed to superior cerebellar artery occlusion, only 39 could be used in the present study. The remainder of the 73 were eliminated for various reasons, the usual one being insufficient detail in the patient's history or on the neurologic examination. About half of the 39 were not examined by us personally, and it was necessary to rely on statements of other examiners. We included only those from whom a reliable examiner had taken a complete history and performed a complete neurologic examination and had also reported them in a complete fashion.

The following analysis is divided into two parts, the first being a study of individual symptoms and the second a division of the cases into groups according to the area of the medulla involved. A survey of the literature will not be undertaken here. The study by Louis-Bar[4] contains a detailed analysis and very complete references. More recently, Krayenbühl and Yasargil[5] have made pertinent remarks and given extensive references.

ANALYSIS OF SYMPTOMS

The usual symptom complex of the Wallenberg syndrome and explanation for the major manifestations are well known and generally accepted. In the following analysis, we would like to consider only those symptoms that are thought to have been insufficiently explained in the past or the explanation for which we believe should differ from that previously suggested.

Sensory loss on face. In all the patients

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tested by reliable observers, pain and temperature sensations were always involved together; one was never affected without the other. Many times it was thought that light touch was affected also. A light wisp of cotton drawn over the face would be felt less well or at least differently on the involved than on the normal side, and discriminatory touch such as two-point tactile and skin writing might be less accurate on that side. When questioned closely about this, several patients stated that the difference was that the cotton did not "tickle" on the involved side but did contralaterally. Walker,[6] using von Frey hairs, demonstrated a decrease of tactile sensation on the face with a lesion of the descending root of the trigeminal nerve.

In all the patients who were accurately tested, the fifth cranial nerve sensory loss was quite anatomic in distribution; this corresponded to the usually accepted descriptions of the cutaneous supply of the trigeminal nerve, although frequently affecting less than all three divisions. In the second section of the present work, it will be seen that one of the more critical factors in determining the anatomic location of the various lesions is the distribution of the fifth nerve loss. In all but a few cases (where no mention was made of its being tested), the corneal reflex was absent whenever the loss of sensation included the upper face.

As the patient improved, it was noted that the sensations of hot and cold returned before the more critical degrees of coolness and warmness. With further improvement, the loss of both pain and temperature sensations often became quite minimal. No definite occurrence of an "onion skin" type of sensory loss was found on the side of the lesion, nor was the motor component of the trigeminal nerve ever definitely involved.

Sensory loss on trunk and extremities. In general, the points mentioned above in reference to sensory loss on the face apply also to that on the trunk and extremities. In the acute stage, hot and cold were lost; with improvement, these returned, but finer degrees of temperature discrimination remained absent. In a few patients, a tendency for delayed perception of pain was noticed on the involved side. The upper limit of the sensory loss was found to be below the neck in most cases. On one occasion, it was noted to be below C_2 and on another below C_4. It usually failed to come to the limits of the fifth nerve on that side. This is consistent with known facts concerning the arrangement of the spinothalamic tract in the medulla, with the sacral segments being more lateral.[7] Many times, the body sensory loss was not tested completely, but, when it was severe and tested fully, it went exactly to the midline. As the sensory deficit improved, the tendency to extend to the midline seemed to decrease, and the residual sensory loss might be found only in the extremities. Neither the arm nor the leg seemed to be especially favored in this regard, with one patient reporting a residual sensory defect in the arm only and one in the leg only. In some patients, the sensory loss on the trunk and extremities became milder as time went on, decreasing so that it was nearly nonexistent after a period of time. From our follow-up data, it appears that, if the sensory loss persisted for more than a month after the onset of the difficulty, it was relatively permanent.

Many patients had learned that, although the sensory loss on the body did not bother them to any extent, they could no longer rely on the affected extremities for testing temperature sensations and thus had to test bath water with the hand or foot on the "good" side.

Spontaneous pain in the face. Facial pain on the side of the fifth nerve involvement is a common feature of Wallenberg's syndrome but one that has received little emphasis, although it was mentioned in some of the original descriptions. Of the 39 patients in the present study, 18 had definite persisting (more than two or three hours) ipsilateral facial pain; 9 others had transitory head or face pain, lasting less than two or three hours. The remaining 12 patients did not complain of pain. It may be, however, that even these 12 may have had pain associated with the onset of their lesion, but it was not severe or was so transitory that they failed to mention it. This is possible because the patients who were questioned directly about the occurrence of pain nearly always answered in the affirmative, even though they had not mentioned it previously. All of 7 patients with pain on the trunk or extremities opposite to the lesion also complained of

ipsilateral face pain. They will be discussed separately below.

The 18 patients who complained of lasting ipsilateral facial pain noted that it was most often in or around the eye and next in frequency in the entire face. Several patients with incomplete lesions noted pain in the area of sensory loss only; this was often limited to the first and second divisions of the trigeminal nerve. Several patients had pain in the ear on the side of the lesion, and others had painful spots on the forehead or cheek. No patient complained of pain in the mandibular or third division alone, without associated pain on the whole side of the face. The pain was usually described as "burning." Other words used were "stinging," "unbearable," and "soreness," and in one case the examining physician termed it "thalamic." The pain usually came on with the onset of the syndrome and sometimes was the first symptom noted, although in some it came on at least two weeks after the onset. One explanation for this delay is that the lesion may be of a progressive nature (and it is true that some of these patients seemed to get worse in an episodic fashion); thus, the pain might be absent at the onset but appear later with more extensive involvement. Another explanation is that the patients who were ill at the onset with nausea, vomiting, inability to swallow, and possibly even pneumonia might not have noticed or complained of the pain at that time; only later when the more severe manifestations had improved would the pain become a prominent complaint. We believe that both of these explanations are possible in some cases.

In some patients, the pain was quite severe. In 8, it was the prominent complaint after the acute phase had passed. In several, it remained for years, and in 1 or 2 patients it worsened and became permanently disabling. Neither Benadryl nor any of the tranquilizers were of help in its treatment. No more definitive therapy was tried. If the pain persisted, so did the sensory loss. In 1 patient, it was thought that there was a definite "thalamic" element to the pain which was especially observed on testing of pain perception; the pinprick caused a dysesthesia with a spreading, painful type of sensation.

Although the pain did persist for years in some, in most patients it generally tended to become milder, either because of regression of the lesion or because the patient became more accustomed to it. Several patients failed to mention it on a return visit but, when questioned directly, said they had pain but had become used to it and had learned to live with it. Some said it was like a sunburn.

The cause of the pain is open to conjecture. In general, the patients without pain usually had less complete lesions of the descending root, such as might be manifested by only a partial loss of pain and temperature, a minimal decrease of the corneal reflex, or a partial involvement of the distribution peripherally. However, some with only 1 or 2 of the peripheral divisions involved had pain.

A consideration of recent work may throw some light on this strange burning type of pain. Bishop[8] summarizes his work and that of others[9] showing the presence of a slow conducting, probably phylogenetically old, multisynaptic pain pathway through the medial areas of the medulla and higher brain stem which ends in the medial thalamic areas (among others). Bowsher[10] has also discussed such a pain pathway. It is believed to transmit slow, burning, delayed pain, such as that which is conducted through the "C" or unmyelinated fibers in the peripheral nerves. This pathway lies in the reticular substance of the medulla medial to the descending root of the trigeminal nerve and the spinothalamic tract. It evidently receives fibers from these 2 tracts.

Assuming the above, how does the retro-olivary lesion cause this burning type of pain? An analysis of our cases seems to suggest that the more complete (and therefore probably deeper) lesions more commonly (but not always) produce this spontaneous pain. One might then postulate either that a *complete* involvement of both the descending root and the reticular pain pathway gives spontaneous pain or that pain results from not as deep a lesion with incomplete involvement and consequent irritation of reticular pain pathway (Fig. 1).

This idea would tend to resolve some of the inadequacies present in older explanations and is consistent with the known facts. Louis-Bar's[4] Case 3 (a patient with spontaneous pain) showed, at autopsy, a very deep lesion that must have involved not only all of the decend-

ing root (at the level shown) but also must have extended into the reticular substance at that level. This case would tend to argue for involvement of the deeper pathway itself plus complete destruction of the superficial as a cause of the pain. The fact that few patients suffer from this type of pain after surgical medullary spinothalamic tractotomy or from surgical section of the descending root of the trigeminal nerve (even though the postoperative pain and temperature loss may be complete) speaks in favor of either an irritation or a complete involvement of the deeper pain pathways as the cause.

Spontaneous pain affecting trunk and extremities. Pain affecting the trunk and extremities opposite to the lesion was noted by 7 patients. In 2 cases, this was described as "burning," once as a "sting." A physician described his patient's pain as being "thalamic," and in the remainder it was simply characterized as "pain." It was noted three times in the leg and arm and three times in the foot only. All 7 patients also had pain in the opposite side of the face. The patient who complained of pain only in the sole of the foot noted that his contralateral pain was limited to the ear. With 1 other patient, pain in the foot was accompanied by contralateral maxillary pain. The onset of these pains was simultaneous with and the duration was usually the same as that of the face pain; they were usually not a cause of prolonged disability.

The explanation of this pain could be the same as that in the face. Why it occurs less frequently than pain in the face is unknown. Crosby[11] believes that it is related to the number of fibers involved; there are probably fewer fibers in the crossed ascending spinothalamic tract than in the descending root of the trigeminal nerve. This would also explain the anatomic location of the pain, which occurred most often in the extremities, as the limbs are represented by more fibers than the trunk. The greater frequency of pain in the lower extremities might be due to the more lateral location of the leg area in the spinothalamic tract. It is thus more frequently involved in a complete fashion, and perhaps the medial areas conducting arm pain are spared. The trunk and extremity pain was likewise unresponsive to Benadryl or other medications.

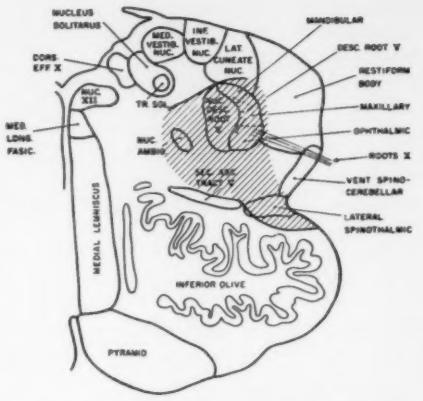

Fig. 1. Hemisection of medulla illustrating area of involvement postulated as necessary to produce spontaneous pain. Medial limits are unknown and possibly deeper than illustrated. Lesion in this case would produce spontaneous pain in ipsilateral side of face (all 3 trigeminal divisions) and contralateral body and limbs, with complete loss of pain and temperature perception in both areas.

Headache and head pain. At the onset of their illness, 9 patients complained of *transitory* headache or head pain. This was always on the side of the lesion and was usually located near the eye or ear. It is difficult to postulate the cause, but it is possibly due to partial interruption of the descending root of the trigeminal nerve. Such pain would disappear when the lesion becomes complete. Headache may accompany the onset of cerebral thrombosis, and Duffy and Jacobs[12] have described pain with thrombosis of the vertebral artery. According to the studies of Wolff,[13] pain with involvement of the vertebral or posterior inferior cerebellar atreries is felt in the ipsilateral posterior occipital and suboccipital regions. Hence it is unlikely that the headache, head pain, and eye and ear pain here considered originate in the arteries involved but are most likely the result of transitory involvement of the descending root of the trigeminal nerve.

Weakness of the face. Of the 39 patients, 22 had some weakness of the face on the side of the lesion; 4 of the 22 were noted to have weakness of a peripheral type, usually mild and not complete, but none had associated

weakness of the ipsilateral abducens nerve. Of the 4, 3 appeared to have more weakness of the soft palate than of the vocal cord. This might be taken to mean that the lesion in these 3 cases was more cephalad than in the usual patient (in whom the weakness of the palate and vocal cord was approximately equal), since the fibers to the vocal cord are thought to come from the most caudal part of the nucleus ambiguus.

The remaining 18 either had weakness only of the angle of the mouth or weakness of a type which was not definitely stated; 13 of these had associated weakness of the same side of the body. Weakness of the face on the side of the lesion did not appear to be associated with the size of the lesion when one considers the rest of the syndrome. In general, judged from other symptoms, it was associated with involvement of the midportion of the lateral medullary area (Fig. 2). The mild facial weakness displayed by these patients usually disappeared fairly rapidly, depending on its degree of severity. However, in some cases, it could be seen several years after the onset of the difficulty. The patients with one exception did not notice the face weakness themselves. The exception was a physician who noticed it in the mirror the day after the onset of his thrombosis.

According to the recent work of Kuypers,[14]

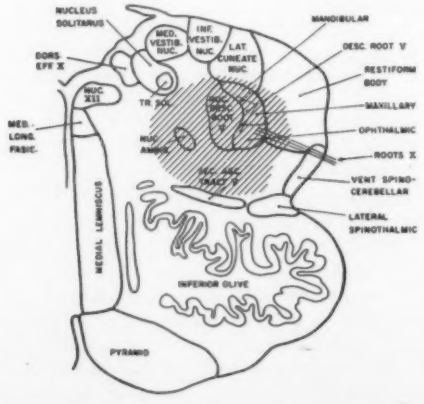

Fig. 2. Hemisection of medulla illustrating postulated area of involvement producing weakness of ipsilateral face, arm, and leg

some of the corticobulbar supply of the seventh nerve nucleus is obtained from aberrant pyramidal tract fibers that come from the pyramid and go dorsally and possibly rostrally to supply that part of the facial nucleus which innervates mainly the lower half of the face. The number of fibers that do this and their distribution as far as the facial nucleus is concerned are quite variable from patient to patient. It is postulated that destruction of these looping fibers causes a minimal weakness of the corner of the mouth on the side of the lesion. Such weakness need not signify an extension of the lesion upward into the pons, although this is the explanation usually given and was shown at autopsy to be the cause in one of Louis-Bar's cases[4] and also has been noted in a case of Karnes, Fisher, and Kubik.[15]

Ipsilateral hemiparesis. Weakness of the same side of the body, including both the arm and leg, was found in 18 patients. In some cases, this weakness was described by the patients as a "paralysis" on that side. However, on testing, only very minimal weakness was found. Since 16 of the patients in this series were first seen between two and fourteen months after the onset of their difficulty, it is possible that a minimal weakness could have cleared by the time we examined them. An additional 2 patients were noted to have weakness on the side opposite to their lesion. The significance of this is not known, but involvement of the pyramidal tract above the decussation is possible; 1 of the 2 had no pyramidal tract signs, and the other, although he had contralateral body weakness, had bilateral pyramidal tract signs. Of the 18 with hemiparesis, 13 also had mild weakness of the face. Except for the case mentioned above, there were no hyperactive reflexes or pyramidal tract signs on the side of the lesion. There was no spasticity; in fact, the tone was usually decreased, possibly due to the cerebellar symptomatology. The arm and leg paresis generally tended to clear up or at least become less bothersome, but some definite weakness could be found in several patients who were reexamined months to years after the onset of their difficulty.

Kuypers[14] has shown that part of the corticospinal tract crosses higher in the brain stem and descends through the dorsolateral region

of the medulla. Again, as with the face, it is possibly the involvement of these fibers that is responsible for the weakness. It might be that the incidence of weakness would have been greater if finer testing had been done and if all patients had been seen soon after the onset of symptoms.

Nystagmus, of course, is common in the syndrome and was present in some degree in 36 patients. It is generally felt that nystagmus in this syndrome is due to involvement of the vestibular nuclei and possibly also of the cerebellar connections.[11] The 3 patients without nystagmus all had lesions thought to be more ventrally placed than usual, and thus the infarct may have not involved the above areas. They will be discussed in the second half of the present work. Of the 36, 17 had rotatory nystagmus. Although this type of nystagmus is mentioned in discussions of this syndrome, little attention has been paid to it. It is possible that some of the remaining 19 had the rotatory type, since, if the examiner did not specifically mention that the nystagmus was rotatory, it was assumed to have been horizontal. In all cases in which notation was made, the quick component of the rotation moved the superior margin of the iris toward the side of the lesion. Thus, the patient with a left-sided lesion and rotatory nystagmus would be found to have the quick component of rotation in a clockwise direction as one looked at the patient. In addition, the nystagmus in most cases was more pronounced when the patient was looking toward the side of the lesion. The rotation was most often brought out when the patient looked in this direction but might also be present with the eyes in any position. It was noted on a few occasions that the nystagmus would be more marked in the eye on the side of the lesion. In several patients, there appeared to be an oblique movement of the eyes. The rotatory nystagmus was found most often in patients with the complete syndrome and less often (as above) in those in whom the lesion was incomplete. It appeared to be closely allied to the symptoms of vertigo and imbalance and less frequently associated with hiccup, pain in the face, or cerebellar involvement (all thought to indicate a large lesion). Although it tended to decrease in amount with time, it persisted for years in many patients.

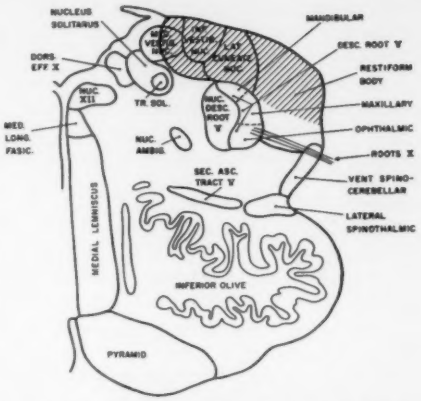

Fig. 3. Hemisection of medulla showing area postulated as being involved in patients with rotatory nystagmus. Note inclusion of medial vestibular nucleus.

Either primarily horizontal nystagmus or nystagmus the type of which was not mentioned was noted in 19 patients. Usually, this was present in both directions of gaze but was often worse when the patient looked in the direction of the lesion. In these patients, no mention was made of the direction of the quick component of the nystagmus. It is felt that the patients with horizontal nystagmus had milder lesions than those with the rotatory type. In addition, it may be that the incidence of rotatory nystagmus indicates the interest and acuity of the observers. The incidence of rotatory nystagmus in those patients seen personally by the authors was much higher than that in the entire series. That is, 20% of the patients examined by the authors had only horizontal nystagmus, compared to 50% in the group as a whole.

Crosby[11] believes that rotatory nystagmus indicates involvement of more than the inferior vestibular nucleus, possibly also of the medial vestibular and other vestibular nuclei as well (Fig. 3). Since the medial vestibular nucleus is medial to the inferior vestibular nucleus, it would be quite reasonable to expect that the deeper and more complete lesions would affect it. Those with rotatory nystagmus are more likely to have more complete lesions and thus probably infarcts deeper in the me-

dulla. It is therefore also possible that the rostral limit of these deeper lesions may be higher than those with only horizontal nystagmus. These conjectures will also have to await pathologic verification. All that can be said at present is that rotatory nystagmus is more often found with complete lesions and that there is no definite evidence of pontine extension of the lesion in these patients.

Diplopia. Of the 39 patients, 18 complained of definite diplopia. Several others complained of blurring of vision at the onset of their "stroke." These later were not included among the 18 because of the unknown significance of this complaint. The double vision usually occurred with the onset of the lesion and tended to clear up in days or weeks. However, a few patients were still troubled with this complaint many years after their "stroke," although it never was incapacitating. The double vision did correlate with possible sixth nerve weakness on the side of the lesion in 6 of the 18. This possible sixth nerve lesion was always very minimal and questionable on examination. The other 12 patients with double vision had no definite third, fourth, or sixth cranial nerve weakness. In addition, the diplopia was not particularly associated with sensory change, face or body weakness, nystagmus, hiccup, cerebellar signs, vertigo, or ninth and tenth nerve loss. The only frequent associated symptom was a marked sense of imbalance at the onset. Crosby[11] believes that the diplopia without specific weakness of ocular movements is due to involvement of cerebellar and vestibular connections to the oculomotor, trochlear, and abducens nuclei causing imbalance in the impulses to the extraocular muscles.

Hiccups developed some time during their illness in 14 patients, at the onset in 7; 1 noted them two days before, and in the remainder they appeared from four days to two months after onset. They were of all degrees of severity and frequency. The usual duration was one to two weeks, but 1 patient had them off and on for four years; 2 patients had hiccups even during their sleep, and 1 patient began hiccupping before he noticed nausea and vomiting. Therefore, hiccup was not felt to be simply a secondary mechanical result of weakness of swallowing and coughing with accumulation of secretions and food in the throat. The patient in whom the tendency toward hiccup lasted four years had them at the frequency of 25 per minute at the onset and 2 to 3 per minute one or two years later. When they finally left him, they had become less and less frequent until he had long intervals of freedom from them.

No therapy was very effective except in 1 patient in whom they were eliminated after bilateral crushing of the phrenic nerves. Fluoroscopic examination was done in 4 patients during the hiccups, and both leaves of the diaphragm were noted to move with the spasms; 2 of the patients had an elevation of the diaphragm on the side of the lesion. Why this should be so is not clear, unless the corticospinal fibers to the phrenic nerve nuclei are mainly ipsilateral at the medullary level.

The anatomic relationships between the symptoms of hiccup and other findings are as follows: Of the 14, 12 had a typically complete Wallenberg's syndrome. None was thought to have a lesion that was more ventrally placed. There was a close correlation between hiccup and marked symptoms of ninth and tenth cranial nerve involvement, fifth nerve pain, nausea, and vomiting. Hiccup seems to be related to a more complete lesion in the middle part of the lateral medullary area. Since hiccup is sudden involuntary inspiration with consequent closure of the glottis, it is postulated that a lesion causing destruction of part of the expiratory area in the medulla could produce, by a lack of balance, involuntary inspiration. It is known that the expiratory and inspiratory areas overlap, the former being larger and also extending more laterally and dorsally in the reticular formation of the medulla[16] (Fig. 4). Whether such a simple explanation could encompass a complicated process in an intricate physiologic mechanism is not known. Perhaps the lack of vagal influence by destruction in this area also plays a part, as has been suggested by Louis-Bar.[4]

Nausea and vomiting. Of the 39 patients, 27 noted nausea and vomiting. These were simultaneous with the onset of the difficulty except in 1 patient, who was so affected two days before his "stroke." They usually cleared up in days or weeks, although 1 patient stated that she continued to suffer from intermittent

nausea and vomiting for two years. They were closely associated in the symptom complex with imbalance, dysphonia, dysphagia, and hiccup and signs of ninth and tenth nerve involvement. Borison and Wang[17] have clearly outlined a vomiting center in dogs which is adjacent to and possibly identical with the nucleus ambiguus in the medulla. We would like to suggest that nausea and vomiting in Wallenberg's syndrome are due to involvement of this vomiting center (Fig. 5). If this is the case, one would expect definite ninth and tenth nerve involvement in all patients with any degree of vomiting, and it is found that these do correlate very well. Those patients who did not have nausea and vomiting, in spite of objective evidence of ninth and tenth nerve involvement, were thought to have superficial or ventrally placed lesions as judged by other findings. It is possible that signs of affection of these nerves in these patients might be due to involvement of their emerging fibers and not of their nuclei. Of the 12 patients without nausea and vomiting, 9 had ventral or superficial lesions and the remaining 3 were seen several months after their onset by observers other than the authors and may not have been questioned closely enough about detailed symptomatology at the onset of their illness.

Remaining symptoms. The symptoms of dysphonia, dysphagia, vertigo, and cerebellar involvement will not be discussed in any detail because our studies add nothing new. They are all reviewed thoroughly by Louis-Bar.[4] One would expect them to be present with lesions in this area, due to involvement of the ninth and tenth nuclei and the restiform body. However, some remarks might be made on the duration and incapacity from these symptoms.

Dysphonia and dysphagia were absent in 10 patients, 3 of whom were seen several months after onset. The other 7 were thought to have superficial or ventrally placed lesions. The dysphonia and dysphagia usually developed simultaneously with the onset of the illness, and the duration varied from nearly complete recovery in three weeks to obvious difficulty for as long as twelve years. It should be noted that several patients stated that they were completely or nearly completely recovered from these symptoms, yet on examination still showed evidence of marked palatal and vocal cord weakness.

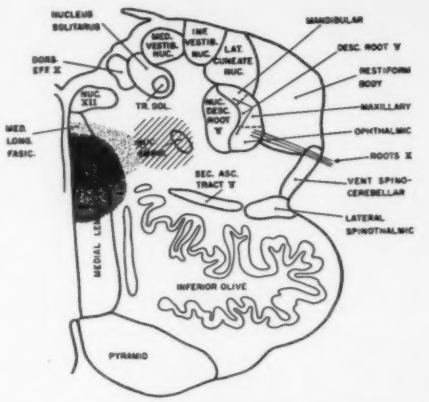

Fig. 4. Hemisection of medulla illustrating possible area of involvement necessary to produce hiccups (oblique lines). Lightly stippled (dorsal) region impinged upon by lesion represents expiratory area of medulla and heavier stippled (ventral) region, inspiratory area.

All patients who were thoroughly tested and had a typical Wallenberg's syndrome also had a typical Horner's syndrome. Some signs of this tended to persist. The pupillary inequality

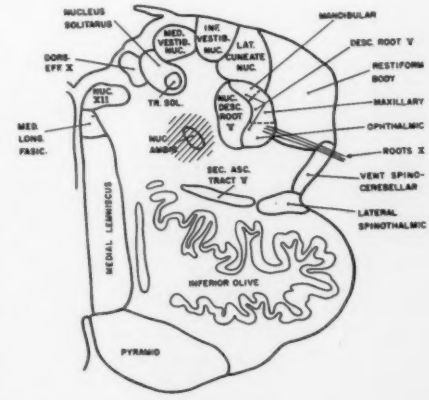

Fig. 5. Hemisection of medulla illustrating possible area of involvement to produce nausea and vomiting. Note complete inclusion of nucleus ambiguus.

could best be seen in a darkened room. Sweating loss also persisted in many patients; 1 patient noted that he had decreased sweating not only on the face and arm but also on the leg on the side of the lesion.

Cerebellar signs were absent in only 2 patients of the entire series; these, however, were first seen four months and ten months after the onset of their illness. Therefore, it is felt that cerebellar signs probably were present in all patients at onset, although certainly they were more pronounced in some than in others. They were always found on the side of the lesion. It is assumed that this difficulty is due to involvement of the restiform body, spinocerebellar tracts, and possibly the inferior portion of the cerebellar hemisphere. Usually, the arm and leg were equally involved. Most patients showed some elements of cerebellar dysfunction involvement even years later, but a few fortunate individuals were found to be normal to testing on follow-up examinations. It is felt that this difficulty was fairly well compensated for by most patients.

It is assumed that infarction of the inferior part of the cerebellar hemisphere will have occurred in some patients and not in others. There is no doubt that the symptoms of ataxia, vertigo, imbalance, nystagmus, and even diplopia and weakness may be in part due to the cerebellar hemisphere involvement, although Fisher[18] feels that such involvement does not have much influence upon the clinical picture.

Miscellaneous comments. Of the 39 patients, 3 had auto accidents or falls two to four months before the onset of their difficulty. It is not possible to say whether these were of importance. Another 3 patients showed definite hypertrophic arthritis on cervical spine radiologic examination. This is possibly of significance in view of the recent emphasis on impingement of the vertebral artery by hypertrophic arthritis of the spine.[19] "Stuffy" nose was noted by 7 patients after the onset of their difficulty. In 1 patient, the stuffiness was on the side of the lesion, 1 noted it on the opposite side, 1 on both sides, and the other 4 patients did not mention the side. A possible explanation of this[11] is that the sensory side of the sneeze reflex arc is interfered with by the fifth nerve loss on the side of the lesion; thus, the patient does not clear his nose completely.

A patient noted that the eye did not water normally on the side of the lesion. In 5 patients, taste sensation was tested; in 3 of these, it was decreased on the anterior part of the tongue on the side of the lesion, and, in 2, no deficit was noted. Taste was not tested on the posterior one-third of the tongue.

Lumbar punctures were done on 12 patients, in most cases several weeks after onset. The cerebrospinal fluid was normal except for a minimal lymphocytosis and total protein values that were usually at the upper limits of normal. Among 27 patients who had roentgenographic examinations of the skull, the only abnormal finding was the presence of hyperostosis frontalis interna in 1 case. In 4 patients who had electroencephalograms, these were within normal limits. A recent study by Friedlander[20] disclosed no consistent electroencephalographic abnormality in this condition. In 3 patients, caloric (labyrinthine) stimulation was carried out; in 2, the caloric response was decreased or absent on the side of the lesion, and in the other patient the response was found to be normal. There was no hearing loss of significance in any of the patients, although several had been moderately deaf bilaterally for some time before the onset.

Summary of duration of symptoms and signs. The duration of symptoms and signs in the typical patient with Wallenberg's syndrome was as follows: Those *symptoms* that were *usually short-lived* and from which recovery was good were marked vertigo, nausea, vomiting, dysphonia, dysphagia, hiccup, and double vision. Half of the patients with fifth nerve pain recovered quickly. Those *symptoms that might persist* were imbalance, mild dysphonia and dysphagia, mild dizziness, and intermittent hiccup. Half of the patients with fifth nerve pain still complained of this long after their acute episode was over. The most common disabling symptom mentioned by the patients on follow-up examination was imbalance, with pain the second most common.

The *signs that were lasting*, although they might show definite improvement, were as follows: fifth nerve sensory loss to pain and temperature, pain and temperature loss over the opposite trunk and extremities, minimal cere-

bellar findings, slight degrees of nystagmus, ninth and tenth nerve paralyses, Horner's syndrome, and ipsilateral loss of sweating on the body and face. The *signs* that *usually regressed rapidly* were face weakness, body weakness, marked cerebellar findings, and marked nystagmus. A recent study by Peterman and Siekert[21] of 35 patients with this syndrome followed by questionnaire gives similar results.

TYPES OF WALLENBERG'S SYNDROME BY ANATOMIC LOCATION

The clinical picture in these 39 patients, when viewed in its entirety, tended to fit into 5 different categories or subvarieties, according to the specific part of the lateral medullary area involved. The critical factor was the site and distribution of the sensory loss. Stopford, by injection studies in 1916[22] and clinically in 1925,[23] attempted to group cases into 3 types on a similar basis.

1. The typical syndrome. Of the 39 patients, 19 had what was considered to be a typical syndrome (Fig. 6). These had ipsilateral loss of pain and temperature on the face and contralateral loss on the trunk and extremities (Stopford's Group I). In general these patients had the more severe symptoms as far as vertigo, nausea, vomiting, dysphonia, dysphagia, face and body pain, weakness of the face, imbalance, and hiccup are concerned. They usually displayed rotatory nystagmus and were more apt to have prominent cerebellar signs.

2. Ventral syndromes. The 13 patients who were felt to have ventral syndromes displayed either no or incomplete involvement of the descending root of the trigeminal nerve on the side of the lesion. These will be discussed in 2 groups.

Of the 13, 6 had involvement of the first and second divisions of the fifth cranial nerve with either no or partial involvement of the third division (Fig. 7); 1 of them showed a decrease in the involvement of the third division as he improved, and another had involvement of the first but only of part of the second division. All had typical loss of pain and temperature sensations on the opposite trunk and extremities. Only 1 of these 6 noticed spontaneous pain, and it was limited to the area of

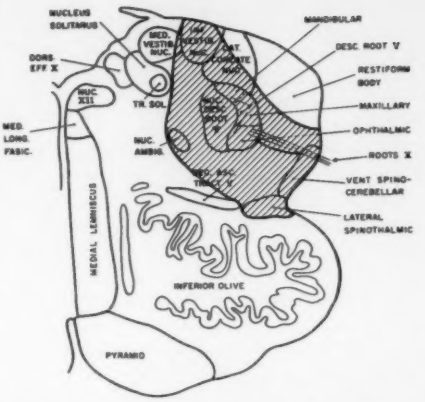

Fig. 6. Hemisection of medulla illustrating typical type of lateral medullary lesion

sensory loss in the first and second divisions. If we assume that, in these 6, the infarct was more ventrally placed than in the usual patient and thus involved only the first and second divisions of the descending root, several things might be expected. Cerebellar signs might be less; nausea, vomiting, hiccups, dysphonia, and dysphagia all might be less; and rotatory nystagmus might be less. This is found to be partially true; 1 patient had no vertigo at the onset, and only 3 of the 6 had

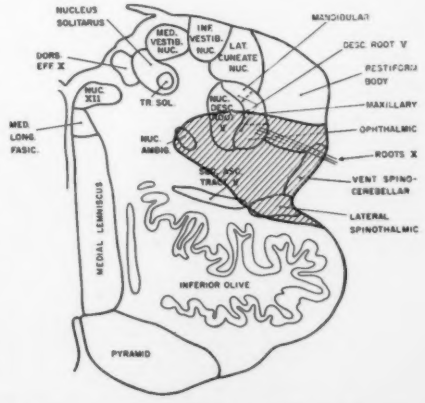

Fig. 7. Hemisection of medulla illustrating extent of ventral type of lateral medullary syndrome

nausea or vomiting. Cerebellar signs were present in the expected number (5 of the 6); 2 had hiccups (the usual incidence). Fewer than would be expected had involvement of the ninth and tenth cranial nerves. Only 2 had weakness of both palate and vocal cord, 2 had a weak vocal cord alone, and 2 had neither. No nystagmus was found in 2 of the patients, which is quite unusual and was never seen in the typical or complete type. Horizontal nystagmus was noted in 2, which might be interpreted as meaning only mild involvement, and 2 had typical rotatory nystagmus. To reconcile rotatory nystagmus with a ventral lesion, one must postulate a lesion of unusual topography reaching from the lateral to the dorsal surface of the medulla but missing the dorsolateral corner.

Even more ventral lesions were suspected in 7 patients (Fig. 8). These patients had no definite sensory involvement of the ipsilateral fifth cranial nerve by history or examination. Some did notice mild subjective ipsilateral numbness of the face, but this soon cleared; 3 had pain in the eye on the side of the lesion at the onset, and 1 had pain in the ipsilateral ear and contralateral foot for two weeks, while 2 had loss of pain and temperature sensation on the upper part of the face on the opposite side. These last 2 are similar to Stopford's Group II. All of these patients had contralateral loss of pain and temperature sensations on the trunk and extremities. The corneal reflex, when affected, was usually lost on the contralateral, not ipsilateral side. This group includes 4 patients who were originally thought to have superior cerebellar artery syndromes. However, it seems much more likely that these are instances of Wallenberg's syndrome more ventrally placed in the medulla, with involvement of the ventral secondary ascending tract from the opposite trigeminal nerve distribution, producing complete or partial pain and temperature loss opposite to the lesion. The fibers for the upper part of the face are more lateral in the ventral secondary ascending tract, and those for the leg are more lateral in the crossed spinothalamic tract. It is therefore assumed that a more superficial (lateral) lesion in this ventral area will give contralateral loss of pain and temperature sensations on the upper part of the face. We believe that these syndromes could not be those of the superior cerebellar artery because all except one had evidence of ipsilateral ninth and tenth nerve involvement. In addition, they all had nausea and vomiting at the onset. None had the tremor sometimes found in the superior cerebellar artery syndrome, and, in fact, cerebellar signs in these patients tended to be minimal, which would be consistent with a ventrally placed lesion in the medulla.

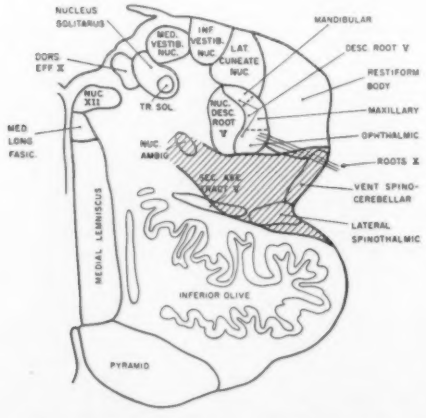

Fig. 8. Hemisection of medulla illustrating lesion less complete and more ventral than that in Figure 7

Other findings in the latter group were as follows: None had hiccups, although 5 had some vomiting. The complaints of dysphonia and dysphagia were sometimes minimal. Cerebellar signs were minimal. The low incidence of hiccup, dysphonia, dysphagia, and cerebellar signs would indicate relative sparing of the more dorsal and lateral areas of the medulla. No weakness of the face on the side of the lesion could be found in 2. None had any involvement of the sixth cranial nerve. While 1 patient had no nystagmus, 3 had horizontal nystagmus and 2 had rotatory nystagmus on upward gaze only. The last are the only 2 patients in the entire series of 39 that had this unusual finding, the significance of which is uncertain. Another had typical rotatory nystagmus on both right and left lateral gaze.

3. Dorsal-ventral syndrome. A lone patient showed involvement of all 3 pathways for

pain and temperature sensations in the lateral aspect of the medulla and thus will be described separately because of the unusual nature of the findings. He had a right-sided lesion with loss of pain and temperature sensations on that side of the face and of the corneal reflex, involvement of the right palate and vocal cord at the onset, dysphonia, dysphagia, vertigo, nausea and vomiting, right-sided cerebellar signs, and right Horner's syndrome. In addition, there was loss of pain and temperature sensations on the entire left side of the trunk, arm and leg, and also of the left forehead. This case corresponds to Stopford's Group III. Horizontal nystagmus present on lateral gaze and very slight weakness of the face on the right and of the left arm were noted. The patient had spontaneous pain in the right face and left arm.

This patient's lesion was unusual in that it included both the dorsal and ventral areas in this part of the medulla and also the most lateral part of the ventral secondary ascending tract of the opposite descending root, producing pain and temperature loss on the opposite side of the face (Fig. 9). When one considers the anatomy of this area, the unusual thing is that this type of lesion does not occur more often.

4. Superficial lesions. It is known that some lesions in this general area tend to be very superficial and involve only the external surface of this part of the medulla to a shallow depth. A case of Louis-Bar[4] illustrated this at autopsy. Of our patients, 5 were thought clinically to have lesions similar to this (Fig. 10). Grouping the patients into this category was done simply on the basis of general lack of severity of the symptoms and findings. After this was done, several things stood out. The fifth cranial nerve loss on the side of the lesion was quite anatomic, but the 4 patients who had spontaneous pain in the face noted it for only a day or two at the most. All had typical contralateral pain and temperature loss on the trunk, but none had spontaneous pain in this area. Cerebellar signs were of a normal degree of severity, and it would be assumed that the restiform body or the inferior cerebellar surface could be completely involved in this superficial lesion. Hiccup only was present in 2 of the 5 patients and lasted only a day in both.

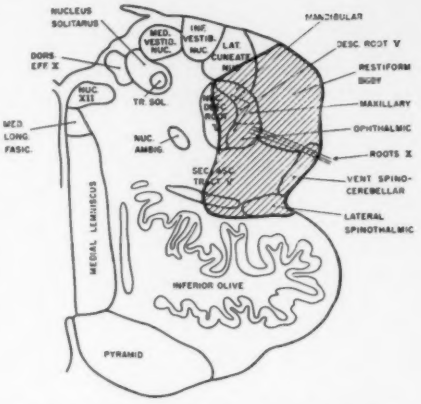

Fig. 9. Hemisection of medulla illustrating dorsal-ventral type of lateral medullary lesion with inclusion of all 3 pain and temperature pathways in this area

The nystagmus was horizontal in 3 and rotatory in 2—a usual distribution. Dysphonia, dysphagia, nausea, and vomiting were minimal, but only 1 patient was found to have no involvement of the palate and vocal cord on examination. Horner's syndrome was present in all cases. These patients with superficial lesions showed a good recovery in all respects and were left with only mild to moderate residual difficulty.

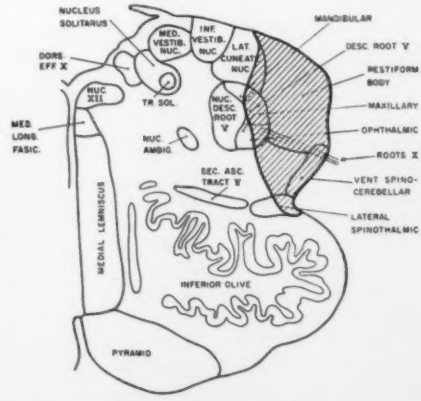

Fig. 10. Hemisection of medulla illustrating superficial type of lateral medullary lesion

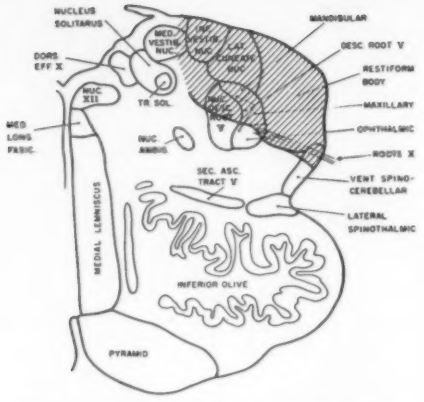

Fig. 11. Hemisection of medulla illustrating dorsal type of lateral medullary lesion

5. Dorsal lesion. Only 1 patient was thought to have predominantly a dorsal lesion (Fig. 11). This was characterized by involvement of only the second and third divisions of the fifth cranial nerve on the side of the lesion. There was no weakness of the ipsilateral face or body. No pain or temperature loss on the opposite side of the body and no spontaneous pain, hiccup, or ninth and tenth nerve involvement was seen. Cerebellar signs were minimal. There was an ipsilateral Horner's syndrome. The patient had vertigo, nausea, and vomiting, lasting only one day. He had rotatory nystagmus more marked in the ipsilateral eye and when looking toward the side of the lesion. We would postulate that this patient's infarct involved only the very dorsolateral corner of the lateral medullary area, affecting the vestibular nuclei (probably the medial and inferior vestibular nuclei), touching the vomiting center but not significantly involving the ninth and tenth nerves, and involving the descending root of the trigeminal nerve only in the more dorsal lateral aspects, that is, the second and third divisions. This lesion forms a nice contrast to those more ventrally placed lesions mentioned above. Interestingly enough, this patient's chief complaint was imbalance. Another interesting fact is that his cerebellar signs were only moderate. Why this should be so with a lesion that possibly involved the restiform body is uncertain. The presence of the Horner's syndrome is also inexplicable in a lesion postulated as lying dorsal to the usual course of the sympathetic pathways.

GENERAL CONSIDERATIONS

This study, unfortunately, has been without anatomic verification, and thus we cannot be sure as yet of one of the points we hoped to prove at the onset, that is, whether most patients with this syndrome had involvement of the posterior inferior cerebellar artery or of the vertebral artery. However, Chason[24] has collected and carried out a pathologic examination on 21 patients with Wallenberg's syndrome. In 19 of these, there was no primary thrombosis of the posterior inferior cerebellar artery but rather involvement of the vertebral artery and generalized arteriosclerosis. The cases summarized by Gerard[25] demonstrated most commonly thrombosis of the vertebral artery at the point of origin of the posterior inferior cerebellar artery, also often with associated thrombosis of the posterior inferior cerebellar artery. Thus, it appears that this syndrome is more one of vertebral artery disease than of the posterior inferior cerebellar artery alone. This has been recently verified also by Karnes, Fisher, and Kubik,[15] who noted vertebral thrombosis in 13 of 17 pathologically proved cases.

The correctness of the present classification hinges principally on the arrangement of the fibers in the descending root of the trigeminal nerve. The results of medullary operations for pain of the face and body have provided a unique opportunity for study of this area, and a recent extensive analysis by Crosby and Yoss[26] sums up our knowledge. We accept the arrangement of the divisions in the descending root as shown in the figures in this study. However, the arrangement of fibers from the most caudal portion of the descending root of the trigeminal nerve as they ascend in the ventral secondary ascending tract is felt by Crosby[11] to result in the "onion skin" arrangement of Dejerine.[27] The fibers carrying impulses from the most peripheral or outer part of the "onion skin" (which includes most of the forehead) ascend, after synapse and crossing to the opposite side, most laterally in the ventral secondary ascending tract, whereas those to the inner portion of the "onion skin"

arrangement, which carry impulses from the nose and mouth area, lie most medially. Thus, the crossed loss of the "first division" in some of our ventral cases may really be the result of involvement of fibers from the broader outer part of the "onion skin." This, on testing, would be hard to distinguish from involvement of the first division of the trigeminal nerve.

We have purposely avoided any discussion of the many vascular syndromes concerned with this part of the medulla over the past century. Recent observers[5] have concluded that the syndromes of Babinski and Nageotte, Cestan and Chenais, and Foix are simply partial, incomplete, or atypical examples of the lateral medullary syndrome. The general feeling and tendency have been to dispense with eponymic designations and minor variations as well as with discussions regarding arterial supply and simply to describe them all as lesions of this corner of the medulla, which is most often but not always supplied by a branch of the posterior inferior cerebellar artery, in itself usually a branch of the vertebral artery.

SUMMARY AND CONCLUSION

Wallenberg's lateral medullary syndrome is analyzed from the viewpoint of its symptomatology, and several symptoms are discussed that have not been greatly emphasized in the past. These include spontaneous pain in the face, trunk, and extremities, ipsilateral weakness of the face and extremities, rotatory nystagmus, diplopia, hiccup, and nausea and vomiting. Various conclusions were drawn regarding the cause and anatomic location of the lesions causing these symptoms.

The anatomic locations of subvarieties of this syndrome were categorized as follows: typical, ventral, dorsal-ventral, superficial, and dorsal. The meaning of this categorization as far as symptomatology and severity of manifestations is discussed.

ADDENDUM: Since this paper was submitted for publication, an excellent study on the same subject by C. M. Fisher, W. E. Karnes, and C. S. Kubik (J. Neuropath. & Exper. Neurol., July 1961) has appeared.

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Studies on hepatocerebral disease

III. Hepatolenticular degeneration in Japan, with studies on copper metabolism

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STUDIES ON hepatocerebral diseases are being widely performed throughout the world. Papers on this subject concerned mainly with abnormalities of copper metabolism have been published previously.[1] In this paper, we report a study of 62 cases of hepatolenticular degeneration (Wilson's disease) in Japan, confirming, in accord with American and European studies, that a disturbance of copper metabolism also plays a major role in the pathogenesis of Wilson's disease in Japan. Similar but rare cases with clinicopathologic findings suggestive of Wilson's disease but without an abnormality of copper metabolism have also been seen.

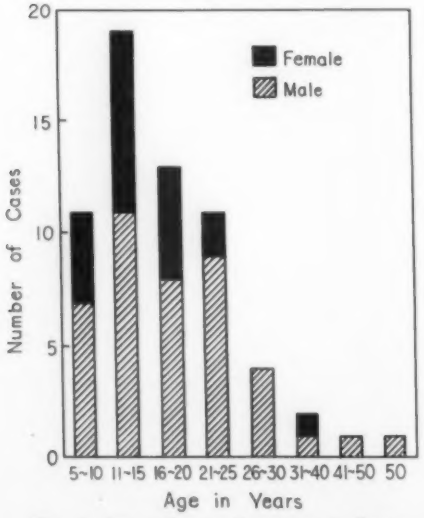

Fig. 1. Age and sex of patients in Japan with Wilson's disease

Wilson's disease used to be considered a very rare disease in Japan. However, much interest was aroused in this disease recently, and 62 cases have been reported in the past ten years. The inference is well grounded that many more unreported cases must be present in this country. The distribution of the patients showed no particular grouping, and the cases were found in almost all sections of Japan.

The heredity of 43 families was investigated in regard to this condition. Familial occurrence of the disease or blood relationship between father and mother of the patient was demonstrated in 15 families, or 35%. In the latter cases, most marriages were between cousins.

CLINICAL FEATURES

Age and sex (Fig. 1). The oldest patient was 55 years of age, and the youngest was 5½ years

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old. Of these patients, 11 were between 5 and 10 years, 19 between 11 and 15, 13 between 16 and 20, 11 between 21 and 25, 4 between 26 and 30, and only 4 were over 40 years of age. Accordingly, 32 patients, or 51.6%, were between 11 and 20 years of age and 58, or 93.5%, were between 5 and 30 years of age.

Of the 62 patients, 41, or 66.2%, were males and 21, or 33.8%, were females. Therefore, the frequency of male patients was twice that of females.

Course of the illness. In 30 autopsied cases, the duration of life from onset to death averaged five to six years but ranged from six months to fourteen years.

Initial symptoms. In 48 patients whose initial symptoms were specifically investigated, the primary manifestations at the onset are grouped in the table.

Statistical studies were performed in 56 cases.

Neurologic disturbances. *Tremor* was found in 47 of the 56 patients, or 83%. Most of them showed a coarse tremor affecting an upper and/or lower extremity or the entire body, and, in some, a coarse movement of flexion and extension of the hand was observed when the arm was stretched in a horizontal position (wing-beating or flapping tremor).

Rigidity. This symptom was noted in 42 patients, or 75%. The affected areas were variable; for example, one extremity, the upper and lower extremities on the same side, all 4 extremities, or the entire body might be involved. Differing from parkinsonism, this rigidity was asymmetric and severe; in advanced cases, peculiar posturing of patients was impressive (Fig. 2). Some patients had attacks of periodic muscle spasm superimposed on the rigidity. This spasm persisted momentarily from several seconds to several minutes. Such momentary spasm may be seen as a myoclonic or tic-like cramp. If there is sustained muscle spasm, the degree of rigidity is markedly increased, and, in proportion to the subsidence of this superimposed spasm, the motility of patients becomes much improved. In some cases of parkinsonism, a similar periodic muscle spasm is observed; for example, the so-called oculogyric crisis. However, the periodic muscle spasm of Wilson's disease is observed more often and is more pronounced.

FREQUENCY OF SYMPTOMS AT ONSET IN 48 CASES OF WILSON'S DISEASE IN JAPAN

	Number of cases	%
Neurologic symptoms	34	71
Abdominal symptoms	11	23
Mental disturbances or personality changes	3	6

Dysarthria and dysphagia. Dysarthria was observed in 34 of 40 patients, or 85%, and, in the more severe cases, their speech could not be understood.

Dysphagia was observed in 15 of 56 patients, or 27%. However, in the group of 18 autopsied cases, this symptom had been pronounced in 15. Drooling of saliva was observed in 15 of 56 patients. Since some patients without dysphagia drooled, this symptom may be caused not only by difficulty in swallowing but also by an increase in salivation. Some patients frequently swallowed saliva, a noteworthy symptom in making a diagnosis early in the course of the disease.

Chorea and athetosis. In 17 of 56 cases, or 30%, choreiform or athetoid movements and posturing were observed. Torsion spasms occurred in 1 patient.

Other neurologic manifestations. Tendon reflexes were increased in 18 of 56 cases, or 32%, and pathologic reflexes were observed in 7 cases, or 13%. A Babinski response was demonstrated in 6 patients. Epileptic seizures were observed in 9 patients, or 16%. Loss of light reflex, nystagmus, and mydriasis and impaired hearing were found in only 2 patients.

Abdominal symptoms. Ascites was observed in 6 of 56 patients, or 10%, and varices of the abdominal wall were found in 4, or 6%. Jaundice was reported in only 1 patient. These data demonstrate that relatively few patients show physical manifestations of liver involvement and their symptoms are in accord with the general tendency of patients with Wilson's disease in America and Europe. A boy whose initial symptom was hepatosplenomegaly is shown in Figure 3. As several previous reports have stated, however, certain liver function tests often show abnormal results. In our series, routine liver function tests were performed in 26 patients, and 22, or 84%, showed abnormali-

Fig. 2. [A, above left; B, above right; and C, below right] A 16-year-old girl with Wilson's disease. Note marked rigidity of asymmetric type and peculiar posturing.

ties in cephalin flocculation, bromsulphalein, or galactose tolerance.

Mental symptoms. Personality changes and emotional disturbances were found in almost all patients. Reminiscent of the description of emotionalism in Wilson's report, many patients showed euphoria, forced laughter, or forced crying. However, mental symptoms at the onset of the disease are rare (see Table). A young female patient who was originally suspected of having schizophrenia because of mental disturbances and catatonic posturing is shown in Figure 4. These personality changes and emotionalism become more and more manifest in the course of the illness. Disturbances in consciousness and coma are seldom seen until the last stage of the illness. This is in contrast with the recurrent type of hepatic coma which is often observed in the course of portal-systemic encephalopathy.

Kayser-Fleischer ring. Kayser-Fleischer's cor-

neal ring was found in 48, or 86%, of the 56 patients.

Endocrinologic and metabolic symptoms. A variety of these disturbances was found in a few patients: namely, gynecomastia in 2, loss of axillary and pubic hair in 2, polyuria in 2, osteoporosis and other bone disorders in 3, abnormal sweating in 2, amenorrhea in several, and atrophy of testes in several.

LABORATORY DATA, ESPECIALLY ON COPPER METABOLISM

As shown in Figure 5, the copper content of urine was markedly increased in Wilson's disease, and the copper excretion was further enhanced by administration of dimercaprol and penicillamine (Fig. 6). Although the serum copper content was somewhat decreased in Wilson's disease compared with controls (Fig. 7), the ceruloplasmin content was markedly decreased, suggesting that the amount of serum copper free from serum ceruloplasmin was relatively increased in this disease (Fig. 8). In autopsied material, the copper content of the liver (Fig. 9) and brain (Fig. 10) was markedly increased, and copper granules could easily be demonstrated in the liver (Fig. 11). In the 18 autopsied cases clinically diagnosed as Wilson's disease, 17 showed disturbances of copper metabolism either clinically by a corneal ring, increase of copper in urine, enhancement of copper excretion by dimercaprol, and decreased ceruloplasmin or in postmortem examination by increase of copper in liver and brain and histochemical demonstration of copper granules in liver. These data in Japanese patients corroborate the reports from American and European countries that an abnormality of copper metabolism plays an important role in the pathogenesis of Wilson's disease.

The one patient in whom no abnormality of copper metabolism was found will be reported in full elsewhere. This 42-year-old man, whose case was complicated by addiction to morphine and alcohol, had a twenty-year history of involuntary movements of the head and a one-year history of rigidity, tremor, dysarthria, and dysphagia. There was no corneal ring. At autopsy, yellow pigmentation and softening were found in the region of the putamen bilaterally, with demyelination, degeneration, and disappearance of ganglion cells in these areas. The liver was cirrhotic, but no copper granules were demonstrated.

Fig. 3. A 12-year-old boy with Wilson's disease whose initial symptom was hepatosplenomegaly

DISCUSSION

Clinical features of Wilson's disease in Japan. As described previously, the clinical features of Wilson's disease in Japanese patients coincide almost completely with those of the patients in America and Europe.[2–6] This is noteworthy because some nervous diseases have shown different clinical manifestations in Japan as compared with other countries. As a representative example, we can cite multiple sclerosis, which had been thought nonexistent

Fig. 4. A young girl with Wilson's disease whose mental symptoms and catatonic posture at first suggested schizophrenia. (By courtesy of Professor H. Akimoto, Department of Neurology and Psychiatry, Department of Medicine, University of Tokyo)

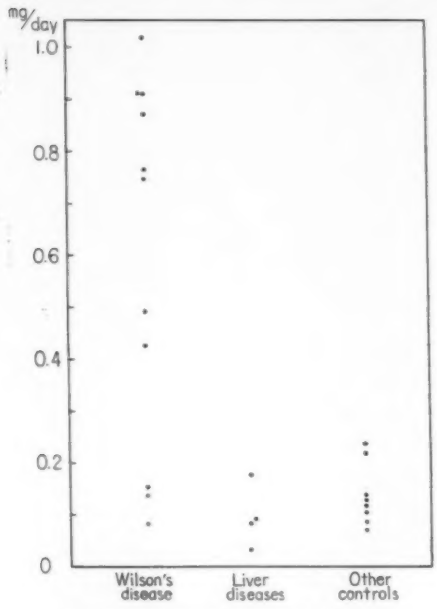

Fig. 5. Excretion of copper in the urine

in Japan until recently, and which is now being investigated with international cooperation.[7] Although we have no accurate data concerning the incidence or prevalence of Wilson's disease in Japan, it is not as rare as had been thought. The frequency of marriage between blood relations is relatively high in Japan in comparison with America or European countries, and this fact seems to contribute to the occurrence of some cases, as shown in the paper. Therefore, the incidence of Wilson's disease in Japan may be equal to or possibly more than that in America or European countries. Consideration of the clinical features of this condition in these countries seems to indicate that hereditary or congenital factors play a greater role in pathogenesis than racial, environmental, or dietary factors. It is reasonable, therefore, that a large number of investigators of this disease throughout the world are taking up the concept of a fundamental error of metabolism as the most pertinent theme of their study.

Role of abnormal copper metabolism in pathogenesis of Wilson's disease. There are many valuable original reports and excellent

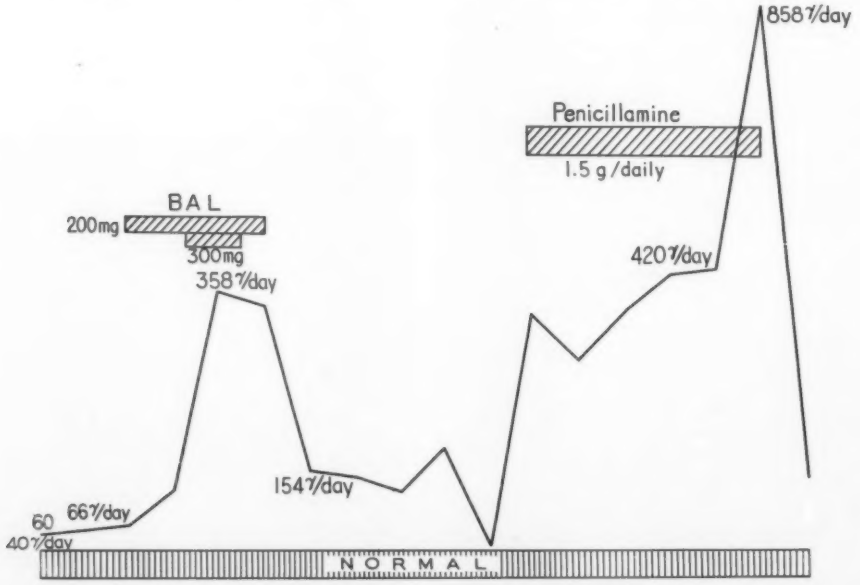

Fig. 6. Excretion of copper in the urine in Wilson's disease

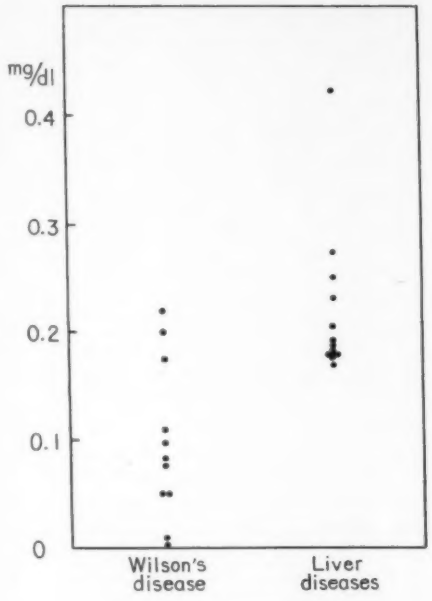

Fig. 7. Serum copper content

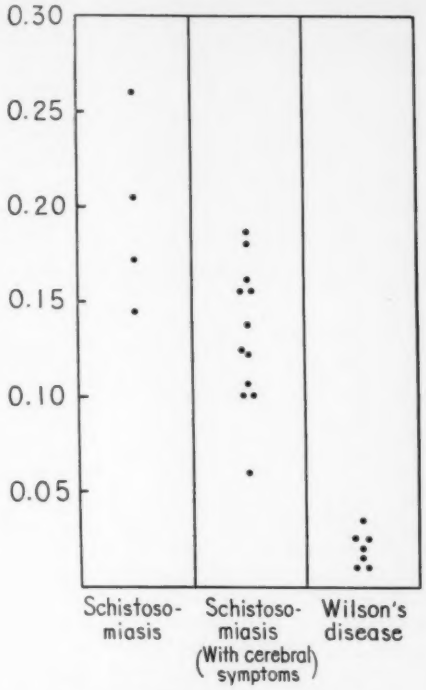

Fig. 8. Serum ceruloplasmin activity

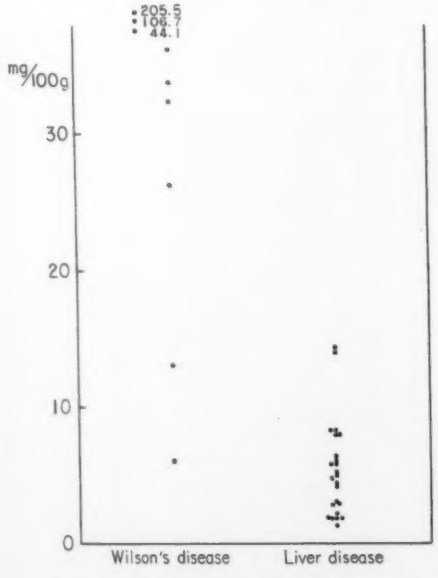

Fig. 9. Copper content of the liver

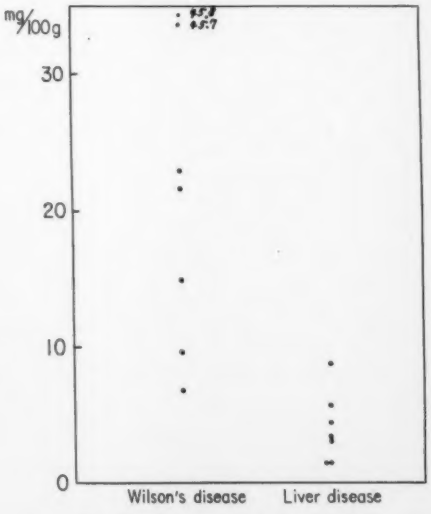

Fig. 10. Copper content of the brain

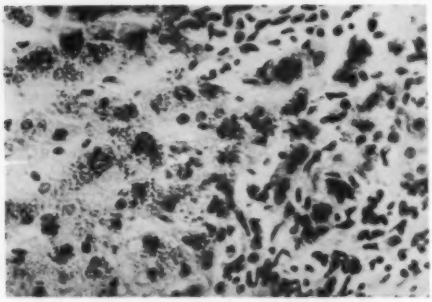

Fig. 11. Copper granules of Wilson's liver. Rhodamine stain

reviews on this subject,[8–13] and we also have contributed to the theory of abnormal copper metabolism from the histochemical point of view.[1] Also, in this clinical and statistical study, the presence of an abnormality of copper metabolism was amply confirmed. We have previously established also that the fetal liver shows similar increased amounts of copper and has positive histochemical findings, suggesting that an increase of copper content is not always abnormal or harmful. However, continuous copper accumulation during postnatal life in Wilson's disease might be responsible for causing the cirrhotic changes in the liver and similarly may cause the degeneration and softening of the lenticular nuclei.

As mentioned before, the presence of an abnormal copper metabolism was demonstrated in 17 of 18 autopsied cases clinically diagnosed as Wilson's disease. These data indicate that a diagnosis established by clinicopathologic findings almost always corroborates with biochemical diagnostic procedures. From the historical point of view, the names of Wilson's disease, hepatolenticular degeneration, and pseudosclerosis are based upon clinicopathologic findings. Recent advances in biochemical investigation have established the association of this classical diagnosis with the presence of an abnormality in copper metabolism.

SUMMARY

1. Statistical analysis of 62 cases of Wilson's disease in Japan and studies on copper metabolism in these cases are reported.

2. Hereditary occurrence of the condition was demonstrated in 15 of 43 families, or 35%.

3. Of the 62 patients, 32, or 51.6%, were between 11 and 20 years of age and 58, or 93.5%, were between 5 and 30 years of age. Frequency of the disease in males was twice that of females.

4. Course of the illness was usually five to six years but ranged from six months to fourteen years.

5. At the onset of the illness in 48 patients, neurologic symptoms were observed in 34, or 71%; abdominal symptoms in 11, or 23%; and mental disturbances or personality changes in 3, or 6%.

6. Statistical studies of major symptoms and signs were performed in 56 patients.

♦ Tremor was found in 47 cases, or 83%; rigidity in 42, or 75%; dysarthria in 34 of 40; dysphagia in 15 of 56; and drooling of saliva in 15 of 56.

♦ Mental symptoms became more and more manifest in the course of the illness and were eventually found in almost all patients.

♦ Physical signs of liver disease were observed in only a few cases, about 10%, while abnormal results of some liver function tests were obtained in 23 of 26 cases.

♦ Kayser-Fleischer's corneal ring was found in 48 of 56 cases, or 86%.

♦ Endocrinologic disturbances were found in some cases.

7. These data demonstrate that the clinical manifestations of Wilson's disease in Japan are in almost complete accord with those in America and European countries. This fact indicates that hereditary or congenital factors play a more important role than racial, environmental, or dietary factors in Wilson's disease.

8. Of 18 autopsied cases, 17 showed disturbance of copper metabolism either clinically by a corneal ring, increase of copper in urine, enhancement of copper excretion by dimercaprol or penicillamine, or decreased serum ceruloplasmin or in postmortem examination by increase of copper in liver and brain and histochemical demonstration of copper granules in liver. The importance of an abnormality in copper metabolism in the pathogenesis of Wilson's disease was confirmed.

9. A case with clinicopathologic findings suggestive of Wilson's disease but without an abnormality in copper metabolism is reported.

We are indebted to the staffs of the following universities and hospitals for supplying us serum, urine, or autopsy materials and case summaries: Hokkaido University Medical School, Department of Neurology and Psychiatry; Akita Prefectural Hospital; Faculty of Medicine, Tohoku University, Department of Medicine and Department of Neurology and Psychiatry; Faculty of Medicine, University of Tokyo, Department of Pathology, Second Department of Medicine, Department of Physical Therapy and Medicine, Department of Neurology and Psychiatry, Brain Research Institute, and Department of Pediatrics; St. Luke's Hospital, Tokyo; Yokohama University, School of Medicine, Department of Neurology and Psychiatry and Department of Medicine; Kanazawa University, School of Medicine, Department of Neurology and Psychiatry; Osaka University, Medical School, Department of Neurology and Psychiatry and Second Department of Medicine; Kobe Medical College, Department of Neurology and Psychiatry; and Faculty of Medicine, Kyushu University, Second Department of Medicine.

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Innervation of spinal dura mater and dura mater of the posterior cranial fossa

Donald L. Kimmel, Ph.D.

SINCE THE STUDIES of Arnold[1] and von Luschka,[2] differences of opinion have existed concerning the origin of the nerves distributed within the dura mater lining the floor of the posterior cranial fossa and whether the spinal dura mater receives a nerve supply. Even the most recent reports on the nerve supply of the spinal dura mater are not in agreement.

There is no question as to the presence of nerves in the dura mater of the posterior cranial fossa; the controversy here concerns the origin of the nerves distributed to this region. These nerves have been described as meningeal rami of the vagus, glossopharyngeal, hypoglossal, spinal accessory, facial, and abducens nerves. Recent clinical studies indicate, however, that the nerves in the dura of the posterior fossa are derived from the upper cervical spinal nerves.

In an attempt to resolve some of the controversies that exist in this area, we have studied the innervation of the meninges and blood vessels of the central nervous system in the human fetus. In this report, we present the results of our investigation which relate to the innervation of the spinal dura and the dura lining the posterior cranial fossa.

MATERIALS AND METHODS

Serial sections of 22 human fetuses ranging between 20 and 106 mm. in crown-rump length were studied in this investigation. The fetuses were fixed in formol-acetic alcohol and sectioned in all the conventional planes. The sections were impregnated by either the Holmes's silver or Bodian's Protargol method. Impregnation was excellent in some of the fetuses, and, in 2 of them, nerve fascicles composed of small nerve fibers destined to remain unmyelinated were impregnated differentially from those containing larger axons which eventually would possess myelin sheaths. To aid in visualization of relations, glass plate reconstructions were made of the nerves and related structures in cervical, upper thoracic, and lumbosacral regions from 3 of the fetuses.

OBSERVATIONS

Nerve supply of spinal dura mater. The nerves distributed to the spinal dura mater are branches of the meningeal rami of spinal nerves (recurrent meningeal nerves, sinu-vertebral nerves). Developmentally, the meningeal rami are first apparent in the upper thoracic levels of the 20-mm. fetus. They are present at all segmental levels in the 47-mm. fetus. At this stage, and in older specimens, 2, 3, and occasionally 4 recurrent nerve fascicles enter each intervertebral foramen (Fig. 1). In the younger fetuses, the meningeal rami at thoracic, sacral, and lumbar levels originate from gray communicating rami or as separate fascicles directly from sympathetic trunk ganglia. In the 47-mm. fetus and older specimens, the meningeal rami at thoracic, lumbar, and sacral levels are joined by fascicles from the spinal nerve trunks (Fig. 1). At an occasional level in the thoracic and lumbosacral regions of the 47- and 66-mm. fetuses, the spinal nerve's contribution to a meningeal ramus can be traced directly from the dorsal root ganglion to the meningeal ramus of the same segmental level (Fig. 1). Similarly, at cervical levels, small nerve fascicles can be

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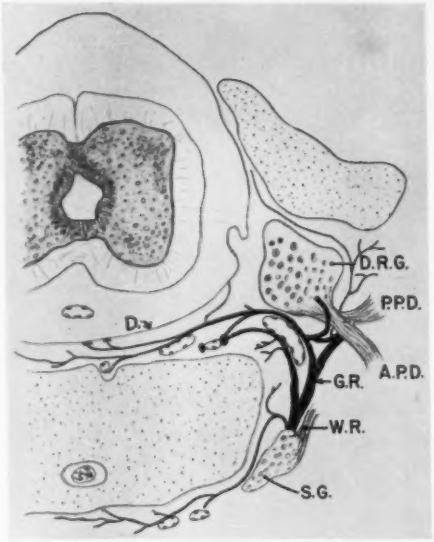

Fig. 1. Reconstruction drawn from several adjacent serial sections to demonstrate origin and distribution of multiple meningeal rami entering an upper thoracic intervertebral foramen in a 47-mm. (9-week) human fetus. Note origin of one fascicle from sensory ganglion, nerves to dura mater, and meningeal ramus lying dorsal to sensory ganglion. A.P.D. = anterior ramus of spinal nerve. D. = dura mater. D.R.G. = sensory ganglion. G.R. = gray communicating ramus. P.P.D. = posterior ramus of spinal nerve. S.G. = sympathetic trunk ganglion. W.R. = white communicating ramus

followed from sensory ganglia to the vertebral nerve which gives origin to the cervical meningeal rami.[3]

Morphologically, the meningeal rami contain two types of nerve fibers. One type is small and lightly impregnated; the other variety is larger and more deeply impregnated (Fig. 2).

Many if not all of the larger nerve fibers in the meningeal rami are processes of sensory ganglion cells. We have been able to trace them from dorsal root ganglia through the distal part of the gray communicating rami and into the meningeal rami at 2 thoracic levels in the 33-mm. fetus. This larger type of nerve fiber also is characteristically present among the many smaller fibers in the nerve fascicles which can be followed from sensory ganglia to the meningeal rami.

At each level, 2 to 4 meningeal rami are present (Fig. 1). Many traverse the intervertebral foramina as perivascular nerves. More follow veins than arteries, and some follow a course independent of blood vessels. In the intervertebral foramina, nearly all the recurrent nerve fascicles lie ventral to the sensory ganglia. At a few levels in the 47-mm. fetus, small recurrent nerves have been identified dorsal to the sensory ganglia. They originate from a plexus[4] of fine nerves situated dorsal to the spinal nerve trunks and are distributed dorsally within the epidural tissue (Fig. 1).

Branches of meningeal rami entering the vertebral canal ventral to the sensory ganglia are distributed medially, rostrally, and caudally in the ventral epidural region. The ascending and descending branches follow the postcentral artery (Fig. 3) and contribute many small nerves to the surrounding epidural tissues.

At cervical and upper thoracic levels, the ascending branches of the meningeal rami are longer than their descending branches (Fig. 4). This is particularly true for the meningeal

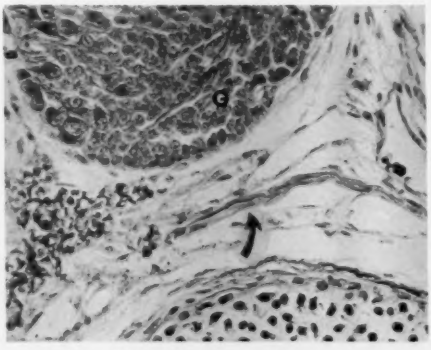

Fig. 2. Photomicrograph showing meningeal ramus (arrow) entering vertebral canal at T1 level of 33-mm. fetus. Note larger, darkly impregnated fibers among numerous small, faintly impregnated fibers. Larger fibers and some small ones are of sensory ganglion cell origin. Other small fibers are postganglionic sympathetic elements. G = dorsal root ganglion. Holmes's silver stain. × 270

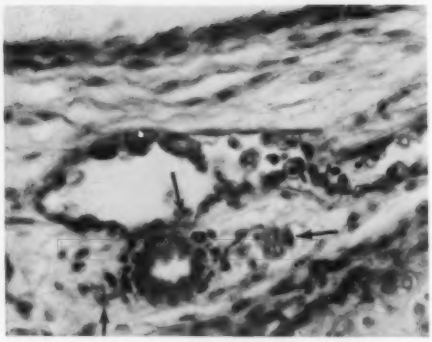

Fig. 3. Photomicrograph showing longitudinally coursing branches of meningeal rami accompanying postcentral artery at first cervical vertebral level of a 47-mm. human fetus. Ascending branch from meningeal ramus of third cervical level is to left of artery (lower left arrow) and ascending branch from C2 is on right. Branches of these nerves continue into cranial cavity to innervate dura mater covering clivus (see figures 5 and 6). D = dura mater. Holmes's silver. × 300

rami of the second and third cervical levels, the ascending branches of which extend through the foramen magnum to supply the dura mater on the floor of the posterior cranial fossa (Figs. 3 through 6). In the lower thoracic and lumbosacral regions of older fetuses studied, the descending branches of the meningeal rami are longer than the ascending branches. At these levels in the 67-mm. fetus (3 months), the ascending branches extend rostrally about one-half segment and the descending branches extend caudally 1 to 2 segments (Fig. 4).

In the cervical and upper thoracic levels of the 33-mm. fetus, the areas of distribution of the ascending and descending branches of meningeal rami overlap those of the meningeal rami of adjacent levels. In the 67-mm. fetus, there is a rostrocaudal overlap in distribution of the meningeal rami at all levels except for the lower 2 sacral and coccygeal segments. In this fetus, the amount of overlap is greatest in the upper lumbar region; here it is slightly more than 2 segments (Fig. 4).

The medial branches of the meningeal rami enter the epidural region located ventral to the spinal cord and dorsal to the vertebral bodies. Branches from the nerves coursing rostrally and caudally on the postcentral artery also are distributed to this region. The latter branches are particularly evident in the intervals between rostrocaudally adjacent intervertebral foramina.

Some nerves in the ventral epidural region follow blood vessels, especially the veins; other nerves in this area course without regard to the vascular elements.

At cervical and upper thoracic levels in the 47-mm. fetus and at all levels in the 67-mm. fetus, some of the nerves in the epidural tissue extend across the midline. At a few levels in the 67-mm. fetus, individual nerve fascicles entering on one side can be followed across the vertebral canal to the region of exit of the spinal nerve roots of the opposite side.

In the older fetuses studied, branches of the

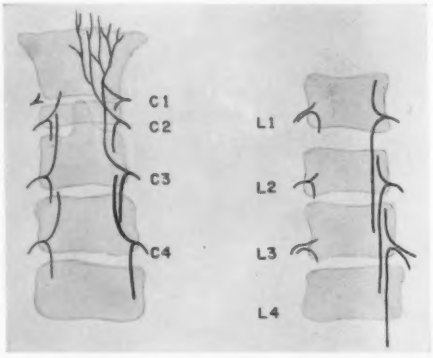

Fig. 4. Graphic illustration showing extent of ascending and descending branches of meningeal rami in relation to vertebral bodies. This drawing was made from glass plate reconstructions of 3 fetuses. Meningeal rami to left of vertebrae, in both cervical and lumbar regions, are drawn from reconstruction of meningeal rami in 33-mm. fetus. Nerves at cervical levels on right are drawn from reconstruction of 47-mm. fetus, and those in lumbar region on right side are drawn from reconstruction of 67-mm. fetus. In older fetuses, with numerous anastomoses between nerves from adjacent levels, rostral and caudal extent of any particular nerve is based upon distribution only of its branches lying along postcentral artery which do not anastomose with nerves entering vertebral canal above or below it.

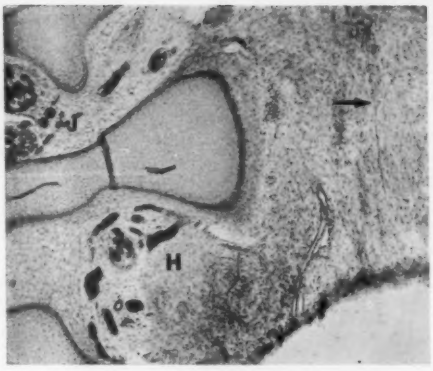

Fig. 5. Photomicrograph showing longitudinally coursing nerves (arrow) in dura mater covering clivus in posterior cranial fossa. These nerves are ascending branches of meningeal rami of upper 3 cervical levels. Midline of fetus is approximately at right edge of photograph, and rostral is toward top of figure. J = jugular foramen. H=hypoglossal canal. Holmes's silver. ×70. Compare with Figure 6.

Fig. 6. Higher magnification of nerves shown in Figure 5. Holmes's silver. × 550

nerves in the ventral epidural region are distributed into the dura mater lying ventral to the spinal cord and with osteogenic buds into the cartilaginous vertebral bodies. A posterior longitudinal ligament has not developed.

In the fetus, the primitive dura mater is a dense cellular membrane situated between the epidural tissue and the subarachnoid space.[5] Ventrally, the dura is 8 to 10 cell layers thick (Fig. 7); laterally and dorsally, it is much thinner, consisting of 2 to 3 cell layers only. An arachnoid membrane cannot be identified.

The nerves distributed within the spinal dura mater are branches of nerves which lie close to the outer surface of the cellular dural membrane in the ventral epidural region (Fig. 7). The nerves entering the dura are very small, ribbon-like fascicles and contain only small, lightly impregnated nerve fibers; 1 to 3 of these nerves enter the spinal dura at each segmental level. They do not follow blood vessels. In the fetal material, most of the nerves enter the thick, ventral portion of the dura mater and are confined to this region in their distribution. A few small nerves penetrate the spinal dura more laterally, in the region of the emerging spinal nerve roots (Fig. 1). Within the dura mater, the nerves divide into smaller branches which ramify in all directions between the cells. The deeper penetrating nerve fascicles extend to the innermost cellular layer of the dura mater (Fig. 7). Definitive nerve endings are not present.

Origin of nerves supplying dura mater lining posterior cranial fossa. The nerves distributed in the dura mater covering the floor of the posterior cranial fossa are derived from the sympathetic trunk and from the upper 3 cervical spinal nerves. They enter the posterior cranial fossa via the foramen magnum, hypoglossal canal, and jugular foramen.

The nerves to the dura mater which enter

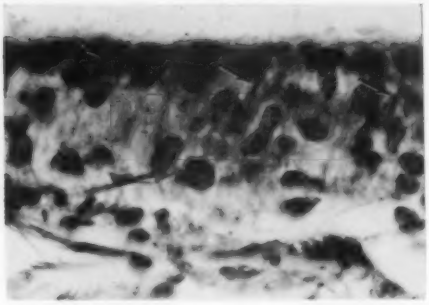

Fig. 7. Photomicrograph showing branches of meningeal nerves (arrows) in dura mater of 47-mm. human fetus. Section is through thick, ventral portion of dura mater at midline of second thoracic segment. Note large nerve in epidural tissue at lower right and its branch entering dura to left. Holmes's silver. × 600

the cranial cavity via the foramen magnum are branches of the meningeal rami of the upper 3 cervical nerves (Fig. 4). Ascending branches from these nerves follow the postcentral artery (Fig. 3) to the level of the foramen magnum. En route, they give off branches to the ventral epidural tissue, the spinal dura mater, and the soft tissues and ligaments surrounding the atlantoaxial joint. At a level corresponding to the rostral end of the odontoid process, branches of these nerves enter the cellular dura mater covering the clivus. There are 2 or 3 of these nerves on each side. Like the nerves in the spinal dura, they contain only small nerve fibers; the greatest number of these are derived from the meningeal ramus of the second cervical level (Fig. 4). Few fibers are contributed by C1. In the dura, the nerves course rostrally, nearly parallel to one another (Figs. 5 and 6). At a few places, a branch interconnects 2 nerves; some of these interconnections are between nerves derived from opposite sides of the body. The nerves which are distributed to this portion of the dura mater extend rostrally almost as far as the region of the posterior clinoid processes (Fig. 8).

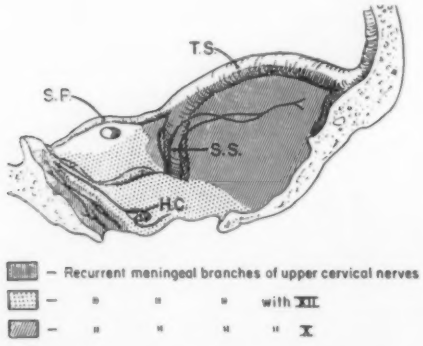

Fig. 8. Diagram of right side of posterior cranial fossa viewed from left showing regions of dura mater which are supplied by spinal nerve branches entering cranial cavity by different routes. H.C. = hypoglossal canal; S.P. = superior petrosal sinus; S.S. = sigmoid sinus; T.S. = transverse sinus

The nerves to the dura which enter the cranial cavity via the hypoglossal canal and jugular foramen are derived from anterior rami of the first and second cervical nerves and from the superior cervical ganglion (Fig. 9). Contributions from these sources unite at the upper pole of the superior cervical ganglion. They form small nerves which are identical morphologically to the meningeal rami of spinal levels; like the meningeal rami, they are composed of numerous small, lightly impregnated nerve fibers and a few larger, more deeply impregnated neuraxes. These nerves follow blood vessels and other nerves to their ultimate areas of distribution. Their terminal branches are distributed within connective tissue and along blood vessels on the undersurface of the base of the skull to the internal jugular vein and to the dura mater of the posterior cranial fossa.

Branches of these nerves distributed to the dura follow the vagal and hypoglossal nerves and the meningeal branch of the ascending pharyngeal artery to foramina through which they enter the skull (Fig. 9). The dural nerve branches accompanying the vagus and hypoglossal nerves lie in the periphery of these cranial nerves among the deeper fibers of their connective tissue sheaths (Fig. 10). Throughout their extent of accompanying these cranial nerves in two of our fetuses, the dural fascicles can be distinguished from the cranial nerve bundles because the dural nerves are of finer texture and are more faintly impregnated

than the fascicles of the vagus and hypoglossal nerves (Figs. 10 and 11).

Accompanying the vagus into the jugular foramen are 3 or 4 dural nerves (Fig. 12). Here, most of them leave the vagus and climb on the wall of the jugular bulb (Fig. 10) which they follow into the skull. Inside the cranial cavity, these nerves course along the wall of the sigmoid sinus (Fig. 13). In some fetuses, 1 and occasionally 2 dural fascicles remain with the vagus to attain the inner aspect of the jugular foramen. Here they join the wall of the sigmoid sinus. None of the dural nerves accompanies the glossopharyngeal nerve into the cranial cavity in our specimens.

The dural nerves entering the cranial cavity via the jugular foramen course laterally and superiorly on the wall of the sigmoid sinus (Fig. 13). A dural branch, which lies on the wall of the sigmoid sinus adjacent to the skull, follows the sigmoid to the transverse sinus and then courses posteriorly along the ventral aspect of this vessel. The other 2 or 3 dural nerves lie on the cerebellar aspect of the sigmoid sinus. They leave this vessel near its lateral end by turning posteriorly, without regard to vascular structures, into the endosteal layer of the dura mater lining the lateral and posterior walls of the posterior cranial fossa (Fig. 8). In the fetal material, these nerves extend toward but do not reach the posterior midline.

Some or all of the dural nerves accompanying the hypoglossal nerve to the skull base leave that nerve in the hypoglossal canal. Here they are joined by branches of a nerve identical in structure and origin which has followed the meningeal branch of the ascending pharyngeal artery to this location. In the fetus, these nerves form a veritable plexus within the hypoglossal canal; (Fig. 11); 2 meningeal rami, other than the fine nerve which continues on the meningeal artery, emerge from this plexus and accompany small veins through the hypoglossal canal into the cranial fossa (Fig. 9). One of these nerves extends anteriorly, the other posteriorly within the endosteal layer of the dura mater along the lateral margin of the foramen magnum (Figs. 12 and 14). Both nerves accompany veins for short distances after their entrance into the posterior fossa.

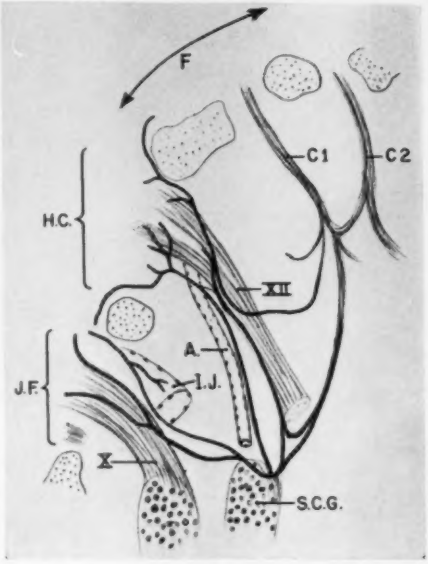

Fig. 9. Drawing made from glass plate reconstruction of nerves distributed to dura mater via jugular foramen (J.F.) and hypoglossal canal (H.C.). Note origin of nerves from loop formed by branches of anterior divisions of C1 and C2 and from superior cervical ganglion (S.C.G.) and their courses with the vagus (X) and hypoglossal (XII) nerves and meningeal branch of ascending pharyngeal artery (A). For clarification, all structures are drawn spread apart more than they actually are in fetus; thus, relations shown are not accurate. Full extent of nerves within cranial cavity is not given. I.J. = internal jugular vein. F denotes arc of cervical flexure with arrows directed rostrally (to left) and caudally.

Terminally, neither follows a blood vessel. The anterior ramus extends into the region of the inferior petrosal sinus and on the medial portion of the posterior incline of the petrous portion of the temporal bone. The posterior ramus is distributed to the posterolateral margin of the foramen magnum and to the medial part of the floor of the cerebellar fossa (Fig. 8).

COMMENT

Von Luschka[2] reports that branches of the sinuvertebral nerves, as he originally named the meningeal rami, do not penetrate the spi-

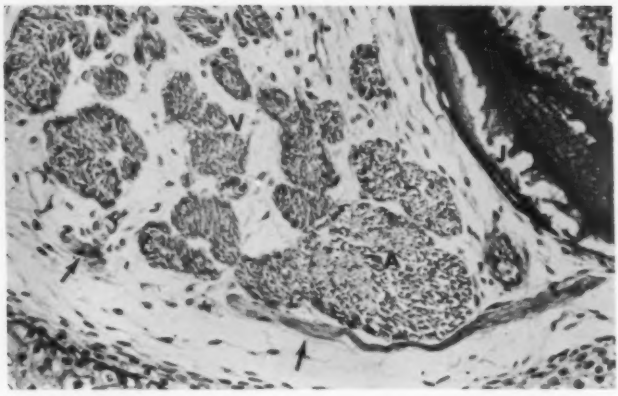

Fig. 10. Photomicrograph showing relations of nerves (arrows) which enter jugular foramen to supply dura mater of posterior cranial fossa to vagus (V) and spinal accessory (A) nerves in jugular foramen. Note branch at lower right leaving vagus and coursing to wall of jugular bulb (J). Holmes's silver. × 300

nal dura mater. He describes nerves which course along the outer surface of the dura, in the ventral epidural tissues, but he was unable to trace branches from them into the dura. Bridge[6] likewise was unable to detect any nerves in the dura of dog and man. His description of nerves lying in the epidural tissue close to the outer surface of the dura mater is similar to that of von Luschka. Arnold,[1] Hovelacque,[7] Pedersen, Blunck, and Gardner,[8] and Stilwell,[4] on the other hand, have found nerves in the spinal dura mater. All of them describe nerves to the ventral dura, and Stilwell states that nerves also enter the dura dorsally.

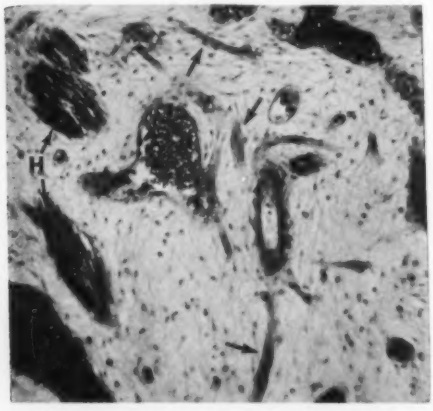

Fig. 11. Photomicrograph showing plexus in hypoglossal canal formed by branches of upper 2 cervical nerves and sympathetic trunk which accompany hypoglossal nerve and meningeal branch of ascending pharyngeal artery (right center) to this region. H = hypoglossal nerve roots. Holmes's silver. × 270

The different conclusions reached by the investigators cited above must result from the quality of the preparations studied. Small spinal dural nerves are not easily demonstrated; they can be seen in the dura in our best preparations only. They cannot be found in the other fetuses where, obviously, their nerve fibers are not impregnated.

The results of our studies on the sites of entrance into the cranial cavity and the manner of distribution of the nerves in the dura of the posterior fossa agree with the observations of Feindel, Penfield, and McNaughton.[9] These authors state that some of the nerves supplying the dura in the posterior fossa are probably derived from the ninth and tenth cranial nerves, but their precise origin is not known. Grzybowski[10] considers them to be recurrent branches of the vagus, as have others.[1,11,12] Nahmmaher[13] thought them to be derived from the sympathetic system, and other authors have described them as originating from the hypoglossal[14] or glossopharyngeal[15,16] nerves. Siwe[17] states that the nerves to the dura of the posterior fossa are derived from anastomoses between the upper two cervical nerves and the ninth, tenth, and twelfth cranial nerves;

Fig. 12. Photomicrograph showing rostral course of one of nerves (arrow to left) distributed to dura mater in lateral part of floor of posterior cranial fossa. This nerve enters posterior fossa via hypoglossal canal and lies in dura mater lining region between foramen magnum and jugular foramen (J). Nerve is derived from first and second cervical nerves and superior cervical ganglion. Rostral is toward top of figure. Arrows to right, in jugular foramen, identify other small nerves derived from upper 2 cervical nerves and sympathetic trunk that accompany vagus to this region. Holmes's silver. × 70

according to Feindel and associates,[9] Rothballer[18] recently has described branches to the posterior wall of the posterior fossa from the second cervical sensory root. Clinical studies very definitely indicate that at least some of the nerve fibers distributed to the dura of the posterior fossa are derived from the upper cervical spinal nerves.[12,19,20]

From our studies of fetal material, we believe that all of the nerve fibers distributed to the dura mater covering the floor of the posterior fossa are derived from the upper three cervical nerves and from the sympathetic trunk. We think that none of them is derived from cranial nerves. We have not observed any nerve fibers from the ninth, tenth, or twelfth cranial nerves joining the nerves distributed to the dura as the latter nerves accompany the cranial nerves through the rostral cervical region and pass through cranial foramina. Nor have we seen any direct branches of the cranial nerves to the dura mater.

It should be emphasized that the nerves entering the posterior fossa via the jugular foramen and the hypoglossal canal do not have a constant pattern (see, for example, the diagrams of Grzybowski's dissections[10]). In the different fetuses, these nerves vary in number and as to the structures they accompany. It is very probable that, in some individuals, one

Fig. 13. Photomicrograph showing nerves (arrows) which supply dura mater of posterior cranial fossa in relation to sigmoid sinus (S). Holmes's silver. × 300

nerve may supply the entire lateral portion of the posterior fossa or that, in another, all the nerves present that supply the dura mater in the posterior fossa may enter the cranial cavity via either the hypoglossal canal or the jugular foramen. Although we have not observed them, one or more of these nerves might accompany the glossopharyngeal nerve in some individuals. In others, none of these rami may accompany a cranial nerve at the inner aspect of the cranial foramina.

Little information can be obtained from a study of fetal material regarding the function of nerves supplying the dura. The nerves are still growing; definitive nerve endings have not developed. Stilwell[4] states that meningeal rami supply sensory and vasomotor nerves to the dura mater. Certainly some of the sensory nerve fibers in cranial dura subserve pain. One might speculate that other sensory nerve fibers in the dura mater may be concerned with pressure regulation and that they constitute the afferent side of a reflex neural pathway which controls blood flow to the capillary beds of the choroid plexuses.

Penfield and McNaughton[12] and Northfield[19] have demonstrated in neurosurgical patients that pressure applied to the dura mater of the posterior cranial fossa produces pain in the occipital, mastoid, and cervical areas. From the results of our studies of the human fetal material, it is now evident that the pressure applied to the dura mater stimulated nerve fibers originating in the sensory ganglia of the upper cervical nerves and that the pain was referred to the dermatomes of these nerves.

Fig. 14. (left) High-power photomicrograph of nerve indicated by arrow to left in Figure 12. Holmes's silver. × 550

CONCLUSIONS

1. The spinal dura mater is innervated by branches of the meningeal rami (recurrent meningeal nerves, sinuvertebral nerves).

2. In the fetus, the nerves enter the spinal dura ventrally. Most of them penetrate the dura near the midline; others enter it laterally near the exiting spinal nerve roots.

3. At each segmental level, 2 or 3 nerves enter the spinal dura mater. They contain only small nerve fibers.

4. Spinal meningeal rami are derived from gray communicating rami (or from the sympathetic trunk ganglia) and spinal nerves.

5. The spinal nerves contribute sensory fibers to the meningeal rami.

6. Several meningeal rami enter each intervertebral foramen. Most of them lie ventral to the sensory ganglia within the intervertebral foramen.

7. Within the vertebral canal, branches of the meningeal rami overlap rostrocaudally and across the midline of the body in their areas of distribution.

8. In older fetuses, at lower thoracic and lumbosacral levels, the descending branches of the meningeal rami are longer than their ascending branches. In cervical levels, the ascending branches of the rami are longer than their descending fascicles.

9. Ascending branches of meningeal rami of the upper 3 cervical levels supply the dura mater on the anterior part of the floor of the posterior cranial fossa. Most of the nerve fibers distributed to the dura in this region are from the meningeal ramus of C2.

10. The nerves supplying the dura mater covering the lateral and posterior walls of the posterior cranial fossa are branches of the first and second cervical nerves and the superior cervical ganglion. They accompany the vagal and hypoglossal nerves and enter the posterior fossa through the jugular foramen and the hypoglossal canal.

The author is pleased to acknowledge the technical assistance of Miss Bobby Sheppard and wishes to thank her for preparing the additional human fetal series in the collection and to thank Mr. Tom Scanlan for the photography.

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Epilepsy in multiple sclerosis

William E. Drake, Jr., M.D., and Donald Macrae, M.D.

As early as 1875, Leube[1] reported the occurrence of epilepsy in a patient with multiple sclerosis. It is inevitable that epilepsy and multiple sclerosis, each not an uncommon disease, will coexist without causal relationship, but there have been sufficient reports in the literature[2–8] to indicate a frequency of coexistence higher than probable by chance. Though a causal relationship appears well established, the literature fails to answer many questions regarding incidence, seizure pattern, prognosis, significance, and clinicopathologic correlation. This failure prompted the present study—a study unfortunately limited, like the others, not merely by the low incidence of epilepsy in multiple sclerosis but also by the difficulties of continuous follow-up. Thus, more questions are raised than answered.

Incidence of epilepsy

In the present series of 289 patients with a secure diagnosis of multiple sclerosis, studied during the past decade, 13 had epilepsy, giving an over-all incidence of 4.5%. In 4 patients, however, an alternate etiology had to be considered.

Case 1. A woman, aged 21 years, suffered a mild head injury one year before onset of the diplopia and left sixth nerve palsy which ushered in multiple sclerosis. The head injury probably caused an alteration of consciousness for a few seconds, but there were no other symptoms or signs. The first epileptic attack, a generalized convulsion, occurred two and one-half years after the onset of multiple sclerosis and six weeks after the onset of a relapse which began with confusion, forgetfulness, and an increased right-sided weakness. During these two and one-half years, 2 relapses occurred, involving brain stem structures.

Case 2. A woman, aged 24 years, was in an automobile accident three weeks before the onset of multiple sclerosis. Although she had no significant injuries, she briefly lost consciousness. The first epileptic seizure occurred nine years later during a relapse which included optic neuritis and sensory symptoms.

Case 3. A woman, aged 27 years, suffered a head injury in an automobile accident and was unconscious for fifteen minutes. Three months later, she had psychomotor attacks and, shortly thereafter, the onset of bilateral leg weakness and diplopia. Despite treatment, the epilepsy remained uncontrolled over the last six years of her illness, while the multiple sclerosis progressed to severe paraplegia and dementia. The total duration of her illness was twenty-four years. She died of pneumonia, and an autopsy confirmed the diagnosis of multiple sclerosis as the only disease process involving the central nervous system.

Case 4. A woman, aged 24 years, had a febrile illness (temperature 106° F.) without neurologic symptoms two years before the onset of multiple sclerosis. The epilepsy, focal motor and sensory attacks affecting the left cheek during a five-week period, started six months after the onset of multiple sclerosis. Three years later, and two days after the onset of another relapse, 5 generalized convulsions occurred in the space of one month. For the subsequent three years, the patient remained seizure-free without anticonvulsant therapy.

Only 3 of these patients had trauma of sufficient severity to make posttraumatic epilepsy probable. In Cases 1 and 3, the diagnosis of multiple sclerosis was confirmed by autopsy. The close relationship of the onset of epilepsy in the remaining cases to exacerbations made multiple sclerosis the more probable cause.

An examination of published reports reveals an incidence of epilepsy varying from 1.4% in Berger's[2] series of 204 cases of multiple sclerosis to 10.8% in Fuglsang-Frederiksen and Thygesen's[7] series of 74. The incidence in the combined series of 1,744 cases averaged 4.1% (Table 1).

Though this incidence relates closely to that in the present series, the divergence is wide

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Read by title at the thirteenth annual meeting of the American Academy of Neurology, Detroit, April 24 through 29, 1961.

TABLE 1
INCIDENCE OF EPILEPSY IN MULTIPLE SCLEROSIS FROM THE LITERATURE

Series	Number of multiple sclerosis cases	Number of multiple sclerosis cases with epilepsy	Per cent of incidence
Berger[2]	206	3	0.4
Bau-Prussak and Prussak[3]	268	13	4.85
Störring[4]	216	13	6.0
Hoefer and Guttman[5]	107	3	2.8
Müller[6]	793	28	3.5
Fuglsang-Frederiksen and Thygesen[7]	74	8	10.8
Feldman[8]	80	3	3.7
	1,744	71	4.1 average

and is probably related to the criteria for the diagnosis of epilepsy. Some authors do not include focal seizures without convulsions, while others may include spontaneous emptying of the bladder or simple faints.

Though the total number of cases available is small, the incidence of epilepsy in multiple sclerosis does seem to be at least 4%—an incidence 8 times greater than expected from the 0.5%[9] in the general population. Moreover, a further correction is applicable. Epilepsy has its onset more frequently in the first, second, fifth, sixth, and seventh decades of life,[10,11] while epilepsy in multiple sclerosis is essentially confined to the third, fourth, and rarely the fifth decades.[12] Allowing for these factors, epilepsy would seem to occur some 20 times more frequently in multiple sclerosis patients than in corresponding age groups of the general population. It is also to be noted that patients with multiple sclerosis are seldom followed to their death, so that the full incidence of epilepsy is not revealed and may be higher than these figures suggest.

SEIZURE PATTERNS

As the nature of an epileptic seizure is not determined by the underlying pathology but rather by the situation of the excitatory lesion and by the susceptibility of the cortex to discharge and spread, it is not to be expected that a particular form of epilepsy might occur in multiple sclerosis. An examination of the attacks does reveal diverse patterns. In the present series, 8 patients suffered general attacks but only 1 without an aura. These auras included automatisms, focal movements, and sensory hallucinations. Only psychomotor or focal motor or sensory attacks were noted in 5 patients.

Thus, a focal cortical discharge could be recognized as either the initial event or the sole event in 12 of the 13 patients, while, in 5 of these 12 patients, there appeared the probability of more than one such focus. This was suggested by the apparent cessation of a particular seizure type and the onset of a different type at a later date, as seen in Case 4.

In 3 patients, this was definitely established; 1 was a woman, aged 22 years, who over a six-month period suffered 6 focal motor attacks affecting the right side of the face. Two years later, during a three-week period, she experienced several sensory attacks, starting in the left side of the face and spreading down the arm and trunk, each lasting several seconds.

An analysis of the literature in this respect is difficult because of details. As far as can be ascertained, in the combined series, 62.3% of the patients had seizures with focal features (Table 2), while Hamlin's[13] Cases 2, 4, and 7 and Bau-Prussak and Prussak's[3] Cases 2 and 3 appeared to have seizures arising from separate lesions in time and place. Of interest is that some 30% of patients had focal motor seizures, although this large figure might, in part, be attributed to selection of cases.

These facts suggest [1] that the epilepsy of multiple sclerosis is predominantly focal, indicating a particular area of cortical discharge,

and [2] that an individual patient may have more than one cortical focus, presumably from an underlying plaque or plaques either at the same or different times.

If these focal attacks are related to local lesions, some correlation between the onset of the epilepsy and the acuteness of the disease and between the focus of seizure and the clinical localization of the disease and electroencephalographic changes might be expected.

In the present series, focal epilepsy without alternate suggested cause and presumably representing the first clinical manifestation of multiple sclerosis occurred in 2 cases. The onset of each condition coincided in 1 case.

In the remainder, the onset of epilepsy was delayed from two months to twenty-three years after the appearance of multiple sclerosis. In 3 patients, apart from the first 2 mentioned, focal epilepsy occurred during clinically quiescent phases of the multiple sclerosis or apparent remissions. In 9 patients, including the 1 with coincident onset, seizure activity coincided 1 or more times with clinical exacerbations.

Of these patients, 7 were examined after the seizure onset, and 4 had neurologic signs localizing a lesion in the area of the cerebrum from which the local discharge presumably arose; the other 3 had grand mal or psychomotor attacks which did not allow lateralization to be correlated with the clinical state. Only the histories of the remaining 6 patients could be analyzed; 2 of these had symptoms of an acute coincident relapse without features to correlate focus and symptoms, while 4 patients appeared clinically quiescent except for the onset of seizure activity.

The literature shows contradictory opinions. Wilson and MacBride[14] stated that they had never seen jacksonian seizures begin after the diagnosis of multiple sclerosis was well established. Störring[4] believed epilepsy manifested itself during the initial stage of the disease. Guillain and Mollaret[15] thought that jacksonian seizures might precede other manifestations of multiple sclerosis, whereas generalized seizures might precede or follow upon the onset of multiple sclerosis. Bau-Prussak and Prussak[3]

TABLE 2
SEIZURE TYPES OCCURRING IN MULTIPLE SCLEROSIS

Investigator	*Number of cases*	*Major and minor motor*	*Focal motor*	*Focal sensory*	*Psychomotor*	*Lapses*	*Faints*	*Atonic*	*Focal and other*
Williams et al.[11]	4		3	1					
Feldman[8]	3	2	2						
Wilson[14]	9	5	3	1		1			? Epilepsia partialis continua
Wilson,[14] from literature	8	2	6						
Nattrass[25]	3	1	1					1	
Lindstrom[20]	1				1				
Fuglsang-Frederiksen and Thygesen[7]	8	1	2	1		1	4	4	2 (empty bladder)
Hamlin[12]	1	1	1		1				
Bronisch[21]	1	1							
Patrick[18]	1		1						
Allen[22]	1					1			
Rich[23]	1	1							
Kass[24]	1	1							
Drake and Macrae, present study	13	2	7	6	1	1			1 (automatic behavior)
Störring[4]	13	6	7	1					3 (auras: epigastric, vertigo)
Bau-Prussak[3]	13	7	3	1	2		1		3 (unreality)
Guillain and Mollaret[15]	4	1	2	1					
Totals	85	31	38	12	6	4	5	5	10

recognized that epilepsy of any type might occur during different phases of multiple sclerosis.

The over-all evidence is that epilepsy may precede or coincide with the onset of multiple sclerosis but occurs more commonly in the course of the disease. Its onset seems a matter of chance, to be related only to the occurrence of a particular lesion in a critical situation in a suitable subject.

It would appear, thus, that [1] epilepsy is occasionally the initial clinical manifestation of multiple sclerosis, [2] the focus of epileptic discharge may at times appear to be related to the clinical situation of a multiple sclerosis lesion, and [3] the onset of seizure activity at times appears to be the sole presentation of an acute relapse clinically otherwise unsuspected, though presumably focal epilepsy in quiescent multiple sclerosis may not represent fresh activity.

The duration of the epilepsy in the present series ranged from three weeks to twenty-four years, and, in 1 patient, epilepsy of three weeks' duration occurred on 2 separate occasions, the focus being in different hemispheres. The duration of 1 type of seizure was less than a month in 6 separate instances, less than six months in 4, one year in 2 patients, and between one and two years in 4 patients.

Only 6 patients required anticonvulsant therapy because of frequency or persistence of epilepsy. Of these, 2 were seizure-free over a two- and three-year period, respectively; 2 died in status epilepticus, 1 six years after the onset and 1 two years after the onset of the first convulsion. Another was uncontrolled for three years and died from pneumonia after a series of grand mal attacks clinically unrelated to a relapse. In 1, the seizures persisted partially controlled throughout the twenty-four years of her illness and were apparently not a factor in her death.

Müller[6] in 1949, reporting the prognosis in 29 patients with seizures, stated that "it would seem as if in disseminated sclerosis, the prognosis of epilepsy is better than otherwise is the case." At reexamination, 15 patients had been free from fits for more than three years. This view appears in part confirmed by the present series in which only 6 patients of the 13 required anticonvulsant therapy. However, in those cases where the seizures persisted uncontrolled beyond two years, prognosis was poor. Although the longest survival was twenty-four years, death was attributable in the remaining 3 instances to status or serial epilepsy.

What appears to maintain is that the epilepsy may be acute or chronic, though the literature does not contain data to test this concept. However, there is close similarity to the traumatic and posttraumatic epilepsy reported by Walker[16] and Phillips[17] in terms of incidence, pattern of attacks, and acute epilepsy; nevertheless, once the epilepsy of multiple sclerosis becomes chronic, the prognosis appears more grave. Moreover, in multiple sclerosis, the over-all prognosis is complicated by the possibility of recurrence from a fresh, acute lesion.

ELECTROENCEPHALOGRAMS

In the present series, an electroencephalogram was obtained in close relation to a seizure in 6 patients. In 5 of these, a gross delta or spiking or theta focus appeared, while 1 showed a generalized dysrhythmia. In 2, the electroencephalographic focus correlated with the clinical focus but correlated three times with the epileptic focus. The relationship of the electroencephalographic changes to the cerebral state is illustrated by Case 5.

Case 5. A woman, aged 36 years, gave a history of frequent relapses and remissions during the preceding five years. During a remission in 1949, when she showed euphoria and dementia, an electroencephalogram showed higher voltage, 5- to 7-cps slowing in the left frontotemporoparietal area.

In February 1955, two months after the onset of weakness with bilateral pyramidal signs, 2 electroencephalograms showed excessive generalized 5- to 7-cps slowing.

In June 1955, the first seizure, an isolated generalized convulsion, occurred during an acute relapse with a left central facial weakness and a dilated left pupil.

In May 1956, a generalized convulsion occurred without other clinical signs. An electroencephalogram showed a gross right, low frontal, anterior temporal, 2- to 3-cps focus.

In September 1956, a generalized seizure was preceded by twitching of the right side of the face.

In February 1957, the electroencephalogram was normal during a clinical remission, while sixteen days later an electroencephalogram showed spiking in the right low frontal anterior temporal area. This was followed by a progressive deteriora-

TABLE 3
RELATIONSHIP OF ELECTROENCEPHALOGRAPHIC CHANGES TO CLINICAL STATE OF PATIENTS WITH MULTIPLE SCLEROSIS AND EPILEPSY

*Electroencephalogram**	*Clinical state*			
	Acute	*Improving*	*Slowly progressive*	*Stationary*
General slowing; theta and delta	4		1	
Focal; theta, delta, or spiking	3		1	1
Both focal and generalized changes	6			1
Normal		2	1	6
Totals	13	2	3	8

*Borderline changes were classed as normal.

tion leading to coma, when an electroencephalogram showed generalized 5- to 7-cps and 3- to 4-cps slowing. Toward the end of 1958, a few brief blackouts occurred, preceded by vertigo. For the subsequent two years, she was clinically improved and seizure-free on anticonvulsant therapy.

This brief case study reveals the variations which occur in one patient, illustrating the multifocal nature of the epilepsy, both from a clinical and electroencephalographic standpoint, confirming the impression that the epilepsy may be related to acute foci and that more than one epileptic focus may occur over a period of time in one patient.

Table 3 shows the relationship of the electroencephalographic changes to the clinical state. While the gross changes are most frequently present in the acute cases, gross changes were seen in 4 records of patients with slowly progressive or stationary disease, suggesting possible acute activity in an otherwise quiescent clinical state.

That a clinically silent lesion might not only be evidenced by a focal seizure but also by a gross electroencephalographic focus is further suggested by the appearance of gross foci in 7% of 184 electroencephalograms of patients with multiple sclerosis during the stationary or slowly progressive phases.

CLINICOPATHOLOGIC CORRELATION

The idea that focal seizures might arise from an area of cortical or other gray matter adjacent to or invaded by the demyelinating process was implied by Patrick in 1918: "In view of the manifold manifestations of multiple sclerosis and of the fact that plaques not rarely invade the cerebral cortex, the only wonder is that such hyperkinesias are not more frequent."[18] In 1925, Kinnier Wilson stated: ". . . the appearance of epileptic symptoms in a patient who is suffering, or is about to suffer (as a sequel shows), from an organic nervous affection so definite as disseminated sclerosis, may legitimately be set down to the change effected thereby on normal cortical function";[14] and again: "For the Jacksonian fits, then, we postulate an underlying basis of actual cortical alteration, and we presume this is constituted by some encephalitic patch, with its accompanying modification of parenchymatous tissue elements."[14] This idea has been reiterated by a number of authors since that time, but, and here again to use the words of Wilson, "as far as we know, in none of the recorded cases of disseminated sclerosis with epilepsy that have been subjected to subsequent pathological investigation has any detailed attempt been made to correlate the clinical and the pathological data."[14]

In only 3 of our cases were autopsies available. One of these was Case 1. A number of her seizures began with her head turning to the right, followed by a right-sided seizure proceeding to a generalized convulsion. The electroencephalogram revealed a left frontal delta focus. The left motor strip and prefrontal cortex were therefore examined in serial sections. Figure 1 shows the areas of demyelination. A number of such lesions immediately adjacent to the cortex were seen. In these areas, the cortex maintained its normal width and appearance, the higher power with the Nissl stain showing the cytoarchitecture immediately adjacent to the demyelinated area to be intact (Fig. 2).

Fig. 1. *(Case 1)* Tissue from the left prefrontal region showing areas of subcortical demyelination. Weil stain. Approximately × 6

There were, in addition, widespread plaque formations throughout the white matter. These appeared more numerous in relation to the ventricles. Lesions were found within the thalamus, globus pallidus, and pons. On microscopic examination, areas of acute neuronal necrosis were found in the temporal lobe (cornu Ammonis and nucleus amygdalae). In addition, there was a disproportionately widespread gliosis of white matter extending into the nondemyelinated areas and involving the basal ganglia and thalamus. A mild degree of microglial proliferation was seen in some areas of the cerebral cortex. The ventricles were all enlarged, as had been noted on pneumoencephalography.

Examination of the second brain (Case 10) revealed 3- to 4-mm. plaques, which tended to be more numerous in relation to the lateral ventricles and the parietal and occipital lobes. Some of the plaques were subcortical and, on histologic examination, were seen to encroach on the cortical structures. Lesions were also found in the thalamus, basal ganglia, pons, and spinal cord. The third brain (Case 3) was not examined by our laboratory, but a complete report was obtained. As in the first 2 cases, the lesions were considered typical of multiple sclerosis.

McAlpine, Compston, and Lumsden[19] felt that involvement of the basal ganglia and thalamus by lesions of multiple sclerosis was not uncommon but that lesions involving the cerebral cortex were less frequent. In view of the clinical picture and these pathologic findings, one is tempted to speculate that cortical or closely adjacent lesions, or lesions involving deep nuclear masses, are responsible for most of the seizures seen in multiple sclerosis. If so, it is without significant alteration of the micro-

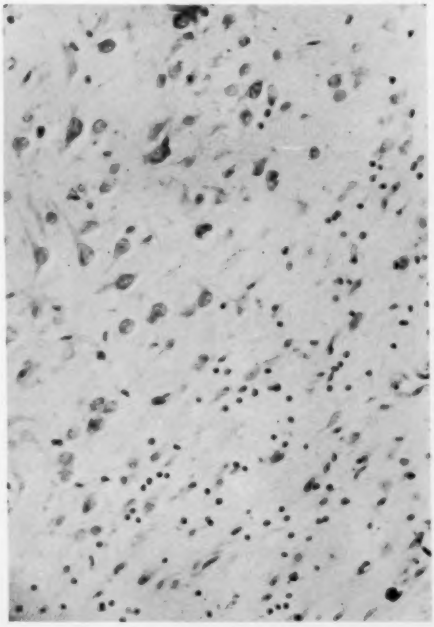

Fig. 2. Cortex adjacent to areas of demyelination in Figure 1, showing normal cytoarchitecture. Nissl's stain. Approximately × 200

scopic appearance of the cortex, except for a mild microglial proliferation. It is possible that the demyelinating process results in an alteration of the local chemical environment of adjacent neurons, thereby making them more prone to spontaneous discharge. This, however, must remain for the time being in the realm of speculation.

CONCLUSIONS

1. The incidence of epilepsy in multiple sclerosis is about 4%, some 20 times higher than expected by coincidence.

2. The seizures are commonly focal and transient but may become chronic and have a poor prognosis.

3. The seizures may precede, coincide with, or follow upon the clinical onset of the multiple sclerosis.

4. The onset of seizures usually coincides with a clinical relapse but may at times be the sole manifestation of an otherwise clinically silent lesion.

5. Electroencephalographic changes are frequently seen during quiet stages of the illness and rarely may suggest the presence of an otherwise quiescent lesion.

6. The probable cause of the epilepsy is an acute demyelinating lesion adjacent to the cortex or in deep nuclear structures.

The pathologic examinations of the brains were done by Dr. Nathan Malamud, Clinical Professor in Psychiatry and Neuropathology, University of California School of Medicine, San Francisco.

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Traumatic arteriovenous fistula of the vertebral vessels

Angiographic demonstration and a rationale for treatment

Neal I. Aronson, M.D.

THE VERTEBRAL ARTERY is rarely injured because of its deep location, relatively small caliber, and the protection afforded by overlying bone through most of its course.

Early experiences with vertebral artery injuries consisted almost exclusively of puncture, stab, and gunshot wounds. These injuries generally produced problems in the management of acute hemorrhage but also occasionally resulted in the formation of traumatic arterial aneurysms. Matas[1] reviewed the world literature on the subject in 1893 and listed 20 traumatic aneurysms of the vertebral artery. It is unlikely that any of these were fistulas, but, since few were carefully studied, this is not entirely certain.

Experience with arteriovenous fistulas of the vertebral vessels coincided with the era of high velocity wounds ushered in by World War I, but cases were very few, diagnostic criteria uncertain, and treatment rather haphazard. In World War II, however, the Surgeon-General of the United States Armed Forces wisely organized army vascular centers for the study and treatment of blood vessel wounds. One of these, under the direction of the late Dr. Daniel Elkin, was able to accumulate sufficient experience to place the diagnosis and treatment of vertebral arteriovenous fistulas on firm ground.[4]

When presented with the case herein recorded, I was unfortunately unaware of Dr. Elkin's contribution, knowledge of which would have resulted in more definitive treatment. I, therefore, believe that it is worthwhile to call attention to this subject once again, so that others faced with similar problems will benefit thereby. In addition, perusal of Krayenbühl's[2] monograph on vertebral angiography and of the literature failed to disclose any other case in which this type of fistula had been angiographically demonstrated, providing a further reason for this report.

CASE REPORT

History. A 23-year-old white male was in normal health until June 1959 when he fell from a truck and struck the left side of his neck against the sharp corner of a box, the blow being delivered to an area just below the left mastoid process. He was stunned and noted immediate stiffness and pain in his neck. As soon as he arose from the ground, he experienced a hissing noise in his left ear and a throbbing of the left side of his neck coincident with each heart beat. He went home and ten minutes later noted marked blurring of vision. This lasted for two to three minutes and then cleared spontaneously. He immediately went to his doctor, at whose office he had an attack of vomiting. Examination revealed contusion of the neck just below the left ear. Roentgenograms of the cervical spine were obtained but were said to be normal. No specific therapy was recommended, and the patient continued to hear the noise, which gradually became louder in succeeding weeks so that it occasionally awoke him from sleep.

On January 14, 1960, he was referred to a neurosurgeon who detected a palpable thrill in the left suboccipital and upper cervical area accompanied by a loud continuous bruit, which could be obliterated by firm pressure opposite the level of the second cervical vertebra on the left. The bruit did not seem to be influenced

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by compression of either or both carotid arteries. For this reason, an arteriovenous fistula of the left vertebral artery was suspected and roentgen studies and surgical exploration were recommended. At this time, the patient was unwilling to submit to further examination and returned to his home. He then consulted a chiropractor who was unable to give him any helpful advice. For the last three weeks prior to his admission, he had experienced some intermittent anterior chest pain in the substernal region which did not radiate and was apparently unrelated to exertion, and he had also noted occasional shortness of breath. He was ultimately referred to me for further evaluation on February 21, 1960.

Examination. The patient was a well-developed and well-nourished athletic 23-year-old white male who was in no apparent distress. Blood pressure was 100/80 on the right and 120/64 on the left; pulse, 64; and respirations, 20 per minute. General physical and neurologic examinations were entirely within normal limits except for the examination of the neck. Here, there was an easily palpable thrill just below the left mastoid process, and, on auscultation, a loud, continuous, blowing murmur with definite systolic accentuation was heard. The bruit was not influenced by compression of either or both carotid arteries but could be obliterated by firm pressure opposite the level of the lateral mass of the second cervical vertebra on the left.

Laboratory data. The hematocrit reading was 43, and the white count was 9,000 per cubic millimeter. Specific gravity of the urine was 1.010, with the tests for protein, sugar, and acetone and the microscopic examination all being negative. Serum urea nitrogen was 15 mg. per cent; carbon-dioxide combining power, 30 mEq. per liter; and chlorides, 105 mEq. per liter. Eagle slide flocculation and VDRL were negative. Blood sodium was 141 mEq. per liter and potassium was 4.5 mEq. per liter. Roentgenograms of the skull and chest were within normal limits, and there was no evidence of cardiac enlargement. Roentgenograms of the cervical spine were entirely normal except that, on one oblique view, the left foramen tranversarium of the atlas appeared to be enlarged. An electrocardiogram was within normal limits. Bilateral carotid and bilateral vertebral angiography were then serially carried out. On the left side, a normal vertebral artery could be visualized up to the level of the arch of the atlas where a fistulous

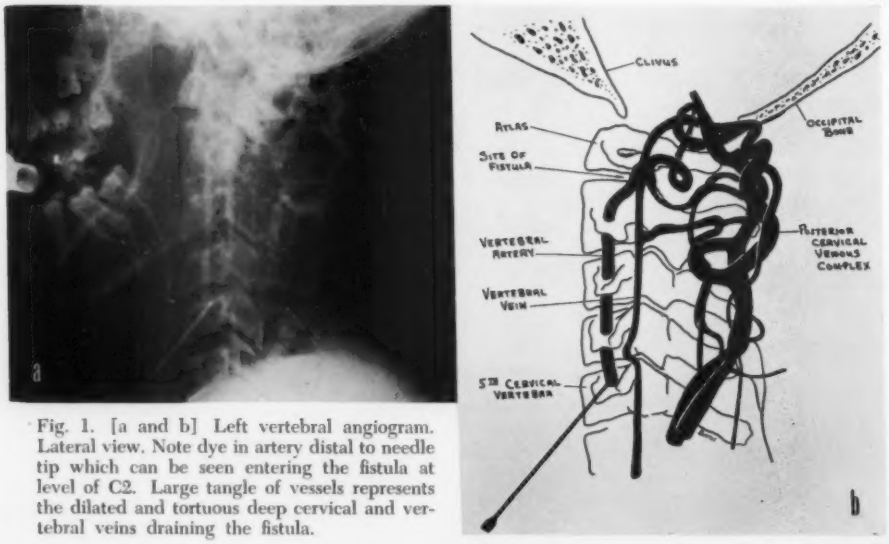

Fig. 1. [a and b] Left vertebral angiogram. Lateral view. Note dye in artery distal to needle tip which can be seen entering the fistula at level of C2. Large tangle of vessels represents the dilated and tortuous deep cervical and vertebral veins draining the fistula.

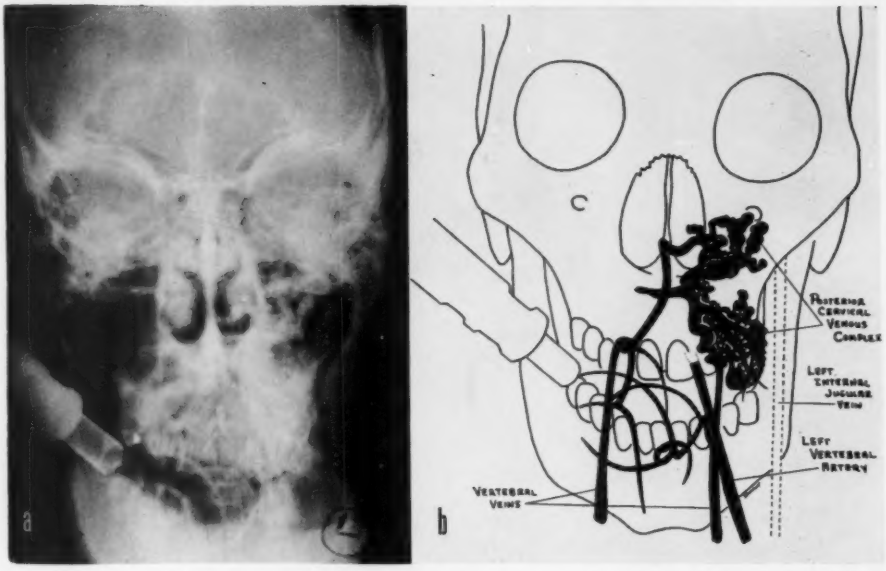

Fig. 2. [a and b] Left vertebral angiogram. Anteroposterior view. Dilated venous tributaries draining the fistula can be seen overlying the left maxillary and antral regions. Note lack of intracranial filling on this side.

communication was demonstrated with a tangle of hypertrophied veins, including particularly the vertebral and the deep cervical veins (Figs. 1 and 2). No dye could be seen entering the cranium above the level of the fistula. Contralaterally, the vertebral study was normal and there was a good demonstration of the intracranial circulation to the posterior fossa (Fig. 3). No communications with the fistula were observed on any view coming from this side. The carotid angiograms were considered normal except for the fact that the occipital artery seemed to be unusually large on the left side, although no evidence of communication with the fistula could be demonstrated. On bilateral carotid injection, there was no evidence of collateral blood flow to the posterior fossa.

Course in hospital. Considerable discussion then ensued as to the safest method of surgical attack upon this traumatic vertebral artery fistula. After careful review of the films, we came to the conclusion that the vertebral artery was probably thrombosed above the level of the fistula, since the malformation did not fill from the right side. The anteroposterior projection of the right vertebral angiogram revealed reflux of dye into the left vertebral for a distance of approximately 1 cm. where it appeared to come to a sharp end above the fistula (Fig. 3). Therefore, proximal ligation of the vertebral artery was considered a safe first step. The possibility of direct surgical obliteration of the fistula was not ruled out, but it was felt that the patient should first be explored under local anesthesia and the effects of temporary proximal occlusion of the vertebral artery determined prior to any other step.

First operation. On March 3, 1960, exploration was carried out under local anesthesia, and the left vertebral artery was exposed at its origin, the vessel being approximately twice normal in diameter. With a stethoscope applied to the area in which the bruit had been audible, a bulldog clamp was then applied to the left vertebral artery. The patient subjectively noted the complete disappearance of the noise in the side of his neck, but, objectively, there was only approximately an 80% reduction

in the audible bruit. For this reason, a second clamp was applied to the left external carotid, which had appeared hypertrophied on angiography, but the bruit was still minimally present. Tapes were also applied to the superior thyroid and the occipital arteries and then, in different combination, occlusion of the various vessels was carried out, but no further reduction in the minimal residual bruit could be obtained. Bulldog clamps were then left in place on the external carotid and vertebral arteries for fifteen minutes, during which time the patient remained alert and cooperative and exhibited no neurologic abnormalities. At the end of this time, auscultation was once more carried out, the bruit no longer being audible. Therefore, double ligation of the vertebral and the external carotid arteries was then carried out, after which the branches of the external carotid were singly ligated with 00 black silk. The incisions were then closed in layers.

The patient did well postoperatively, but, three days later, a slight bruit had returned and was audible to the patient when he placed his fingers over his ears.

Second operation. On March 7, 1960, under general anesthesia, via a posterolateral approach, the left vertebral artery was exposed above the arch of the atlas and ligated with 2 silver clips. After this procedure, exploration in the region of the fistula was carried out between the transverse processes of the atlas and axis and many dilated, thin-walled venous channels were obliterated by coagulation and clipping. This posterior approach, however, did not facilitate definitive handling of the fistula.

Postoperatively, the bruit again reappeared very faintly but was no longer subjectively audible at the time of discharge on March 12, 1960.

The patient was seen in the clinic four months later. He was no longer troubled by the bruit but could hear it faintly when he covered his ears, and it was still audible objectively, although quite faintly. He had no other symptoms of any kind and was working full time. The possibility of attempting to completely obliterate the fistula was considered, but the patient declined, stating that his symp-

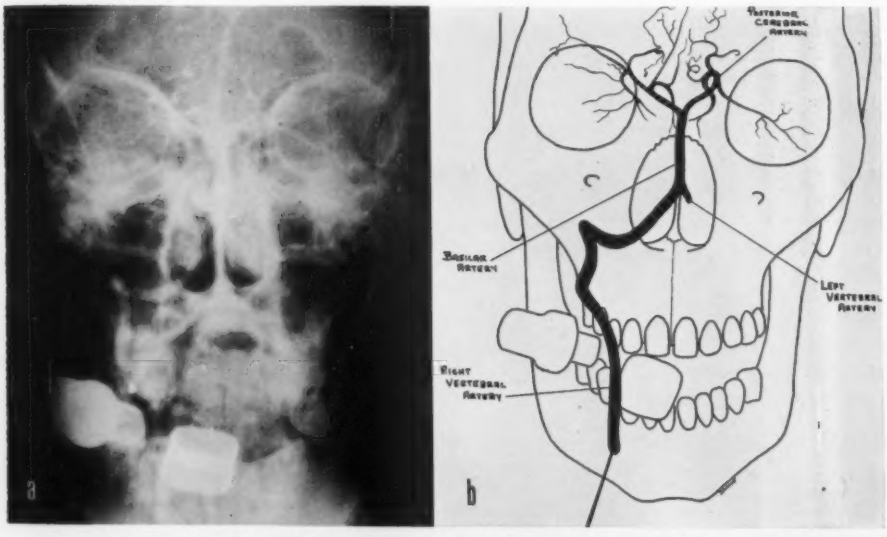

Fig. 3. [a and b] Right vertebral angiogram. Anteroposterior view. Normal course of right vertebral artery with filling arteries of the posterior fossa. There is no evidence of retrograde filling of the fistula on contralateral side of neck.

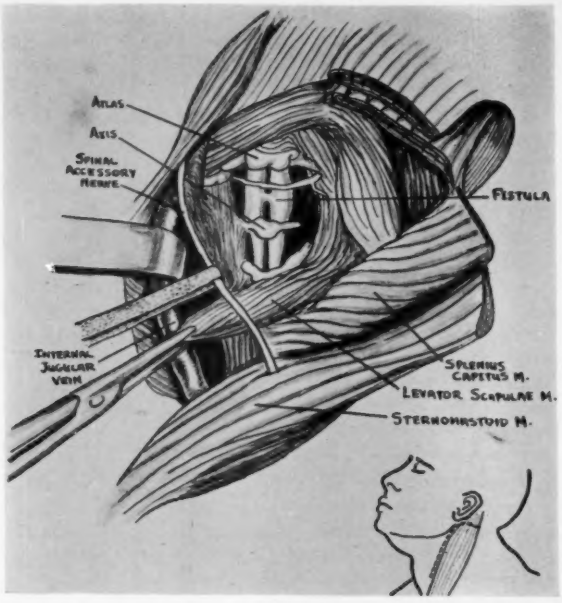

Fig. 4. Lateral approach to vertebral artery in upper portion of neck. Redrawn from Elkin and Harris. For description, see text.

toms were no longer sufficiently troublesome to warrant the operation.

DISCUSSION

Management of vertebral arteriovenous fistulas has been difficult not only because of their rarity but also because they have frequently been misdiagnosed as involving the carotid vessels, with resultant ineffectual or catastrophic ligation of the latter arteries.[3] Clinically, the differentiation can be made by the failure to obliterate the bruit by compression of the carotid arteries in the case of fistulas involving the vertebral arteries, as illustrated in the foregoing case. Another reason that effective treatment has lagged somewhat is fear of occluding the vertebral artery because of its vital role in brain stem irrigation. Finally, there has been the mistaken belief that proximal and distal ligation of arteries having few collaterals would effectively obliterate fistulas in their course.

Until the report of Elkin and Harris,[4] these were, to a large extent, unsettled questions.

As late as 1836, Sanson had declared that the vertebral arteries were so hidden and inaccessible as to be beyond the reach of surgery. It was not until 1852 that the vessel was successfully ligated for a gunshot wound by Maisonneuve and Favrot.[5] The next notable advance was the successful excision of a traumatic arterial aneurysm of the third portion of the artery by Matas in 1888.[1] Matas noted that this was the only case of a vertebral artery wound or aneurysm seen among 463,894 patients admitted to the Charity Hospital from its opening in 1832. Although Makins[6] observed a number of arteriovenous fistulas among war wounds in the British forces in World War I, none involved the vertebral vessels. There were, however, 3 traumatic arterial aneurysms of the vessel, 1 of which was surgically cured by packing and proximal ligation at the hands of Colonel Harvey Cushing. Küttner,[7] however, was able to collect 7 aneurysms from German war casualties of World War I, 2 of which were arteriovenous. Some years later he observed a third,[8] and Bier, Enderlin, and Justi were each reported by Perrig[3] to have noted 1 example. Apparently, these were unsuccessfully managed either due to clinical misdiagnosis or lack of definitive treatment.

Elkin and Harris[4] were able to collect 10 cases of traumatic arteriovenous fistulas of the vertebral vessels from the United States Armed Forces in World War II, and they are to be credited with the evolution of the rational management of this condition. Of their 10 cases, the fistula was located in the first portion of the vessel in 1, the second in 6, and the third in 3. The diagnosis was correctly made preoperatively in 5 patients on the basis of a continuous bruit with systolic accentuation and failure to obliterate it by carotid compression. Their original approach was much as my own, but they quickly found proximal ligation of the vertebral and/or occlusion of the external carotid to be ineffectual. Then, adopting Henry's[9] lateral approach to the vertebral artery, they were able to expose the fistulas of the second or third portion of the vessel directly and clearly. When the fistula was located high in the neck, the exposure was accomplished as shown in Figure 4. An incision was made anterior to the sternomastoid muscle and carried upward and then posteriorly to the mastoid process. The sternomastoid and splenius capitis muscles were divided from their attachments to the skull and retracted posteriorly. The spinal accessory and upper cervical nerve roots were isolated and preserved, the carotid sheath retracted anteriorly, and the origins of the levator scapulae muscle divided from the transverse processes with a periosteal elevator. The roofs of the transverse foramina were then ronguered away in the region of the fistula. Lower in the neck (Fig. 5), the approach was essentially the same but was carried out between the heads of the sternomastoid muscle. If the fistula was situated still lower, in the first portion of the vessel, they found it helpful to resect the medial portion of the clavicle. After full exposure of the fistula was accomplished by one of these approaches, it was followed by excision, mass ligation, packing, or proximal and distal ligation of both its arterial and venous tributaries. Multiple attempts were occasionally necessary. Their one case of fistula of the first portion of the vessel arose near its origin from the subclavian and was approached through a combined transverse supraclavicular and vertical incision and totally excised after isolation of all tributaries.

Interestingly, only one of their cases, as mine, was the result of a closed injury, all others being due to shell fragments or gunshot

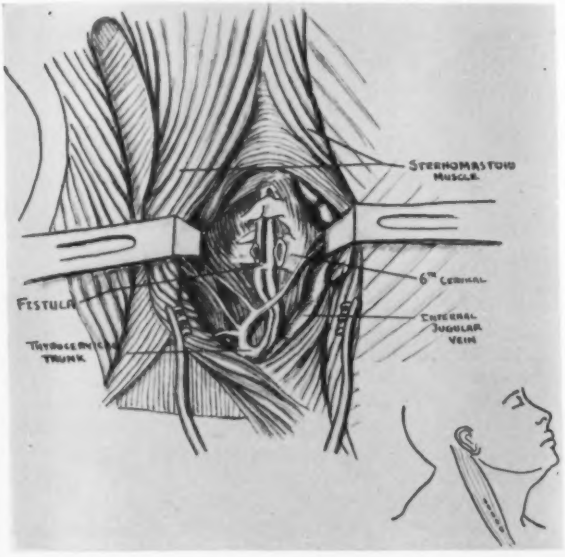

Fig. 5. Lateral approach to vertebral artery in lower portion of neck. Redrawn from Elkin and Harris. For description, see text.

wounds. In this case, a soldier was struck on the side of the neck by a falling log and a subjectively and objectively audible bruit developed. Operation disclosed the fistula at exactly the same site as that noted in the present report. This suggests that there may be anatomic factors which render the vessel prone to injury in the region between the atlas and axis when a blunt force is brought to bear on the side of the neck.

A review of reports of previous operative intervention upon the vertebral artery for any condition reveals a mortality rate of well over 50% prior to the contribution of Elkin and Harris[4] whose 10 cases of traumatic vertebral fistula were operated without mortality or significant morbidity. Furthermore, all were cured of their fistulas, a tribute to skillful management provided by these men.

It would appear that angiography may play a vital role in firmly establishing the diagnosis of this condition, in demonstrating the exact site of the fistulous communication, and in determining the collateral circulation which exists. In retrospect, it is obvious that arteriographic study of the patient reported herein provided sufficient information with which to proceed immediately to a direct obliteration of the fistula had one then been aware of the best approach by which to accomplish this. Faced with a similar problem in the future, I would probably still elect to temporarily occlude the vertebral artery near its origin under local anesthesia in order to test the sufficiency of collateral circulation to the brain stem. Having satisfied this point, however, one could then immediately proceed to expose the fistula by the lateral approach and excise it or obliterate it with ligatures.

SUMMARY

1. A case of traumatic arteriovenous fistula of the vertebral vessels is presented and the pertinent literature reviewed.

2. Arteriographic verification of the lesion is presented.

3. A rational approach to the diagnosis and treatment of this condition is suggested based upon previously established principles and modified by the valuable data provided by arteriography.

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Cerebral cysticercosis in Mexico

Luis Lombardo, M.D., and Jose Humberto Mateos, M.D.

THIS PAPER is a preliminary report of a comprehensive investigation of cerebral cysticercosis, or infestation of the human brain by the embryologic form of Taenia solium.

The interest which this disease has aroused among the Mexican neurologists for several years derives from the great incidence of this disease in our country.[1] Some idea of the incidence is apparent from the available statistics. Dr. I. Costero[2] reports an occurrence of 3.6% of cysticercosis in all autopsies performed in six consecutive years in the General Hospital. The Pathology Unit of the School of Medicine in Mexico City reports an incidence of 2.6% of this disease in 2,202 consecutive autopsies.[3]

The following is a study of 31 cases seen in the new Neurological and Neurosurgical Unit of the General Hospital in Mexico City during its first year of operation from January 1959 through December 1959. During this period, 265 patients with a wide variety of neurologic disorders were admitted to the Service. The 31 patients with cysticercosis represented 11% of the total admissions. Also, during this time, 46 craniotomies were performed for all varieties of intracranial disease; 13 were in patients with cysticercosis, representing 35% of all craniotomies.

CLINICAL PICTURE

The diagnosis of this disease is difficult when the great variability of clinical findings is taken into consideration. The factors that contribute to this variability are the acuteness or chronic state of the infestation, the number of parasites and their location, and the reaction of the brain structures to the presence of the cysticercus.[4,5]

In general, one can divide the analyzed cases into 4 main groups which can be correlated with their anatomic location:

1. Cases without symptoms
2. Cases with localizing signs
3. Cases with signs of increased intracranial pressure
4. The mixed types (signs of increased intracranial pressure and localizing signs).

Cases without symptoms. In these, one or several parasites are found in the cerebral parenchyma or in the meninges without any history of neurologic disability. The diagnosis is made solely on the basis of autopsy findings. Symptoms are lacking, presumably because of the location of the parasite in clinically silent areas of the brain.

Cases with localizing signs. One or several parasites, occasionally hundreds of them, are found in the brain parenchyma; these produce symptoms dependent upon their location. They appear in the form of focal convulsions, motor or sensory changes, and so forth. The cases in this group represent the parenchymatous type of cysticercosis (Figs. 1 and 2).

Cases with signs of increased intracranial pressure. The symptoms in these cases are the result of obstruction of cerebrospinal fluid circulation in the ventricular system or in the subarachnoid spaces. This type corresponds to the ventriculosubarachnoid form[6,7] (Figs. 3 and 4).

The mixed types. These are by far the cases most frequently seen. In these cases, a combination of signs of increased intracranial pressure and localizing signs are the result of the location of the parasite in the brain parenchyma and the blocking of circulation of the cerebrospinal fluid[4,8,9] (Figs. 5 and 6).

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Read at the twelfth annual meeting of the American Academy of Neurology, Miami Beach, April 25, 1960.

Fig. 1. Cysticercus cellulosae with calcified scolex located in corpus callosum above lateral ventricle

This disease can affect any individual regardless of sex or age. However, in our series, the usual onset was in the first and second decades of life, without predominance of either sex. Most of the patients (27 cases) were admitted to the Service with a diagnosis of increased intracranial pressure. Among those admitted, headaches, nausea, vomiting, and decrease of visual acuity were the most common symptoms. The presence of papilledema confirmed this impression in 25 patients. Other signs and symptoms, such as motor and sensory disturbances, convulsive seizures, changes in the visual fields and mental changes, were also present in these patients.[8,10] Table 1 illustrates the frequency of these findings.

The complementary procedures which were utilized in the studies of these cases were:

1. Electroencephalogram. This study was performed in 28 cases. In 19, slow generalized activity was reported; in 5 cases, focal abnormalities were seen. All others were described as normal.

2. Radiologic studies. *Roentgenograms* of the skull were taken in all cases. In 9 instances, changes in the sella turcica were reported (enlargement, destruction of clinoids, and so forth). In 3 other cases, additional signs of increased intracranial pressure, such as separation of the sutures and marking of the convolutional pattern were described. In 3 instances, the presence of multiple small round calcifications with a "shotgun" appearance was revealed. This finding is characteristic of the disease.

Contrast studies with air were done in 27 cases; 26 of these were ventriculographies. In 9 cases, fractionated pneumoencephalography was also necessary. When blockage of the ventricular system was discovered, iodoventriculography was performed to localize the exact

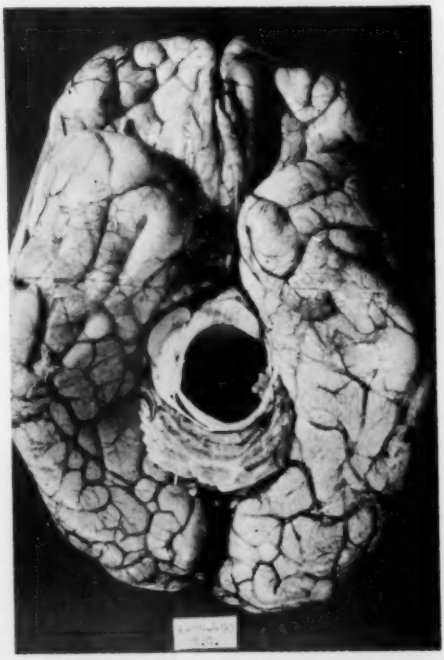

Fig. 2. Large cysticercus producing destruction of midbrain

Fig. 3. Basal meningitis with cyst formations adhering to pons

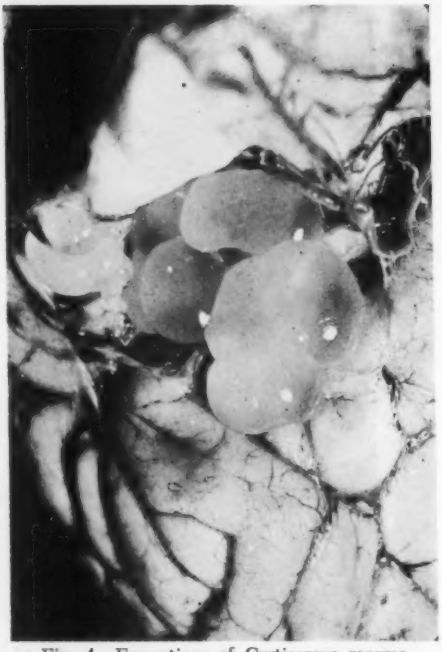

Fig. 4. Formations of Cysticercus racemosus in subarachnoid space in sylvian fissure

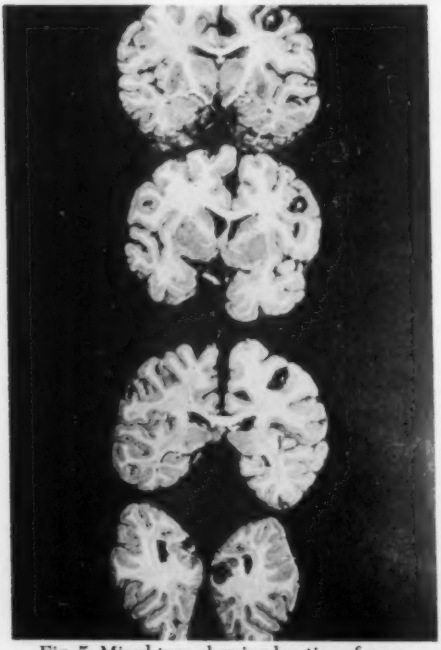

Fig. 5. Mixed type showing location of parasite in parenchyma and subarachnoid space

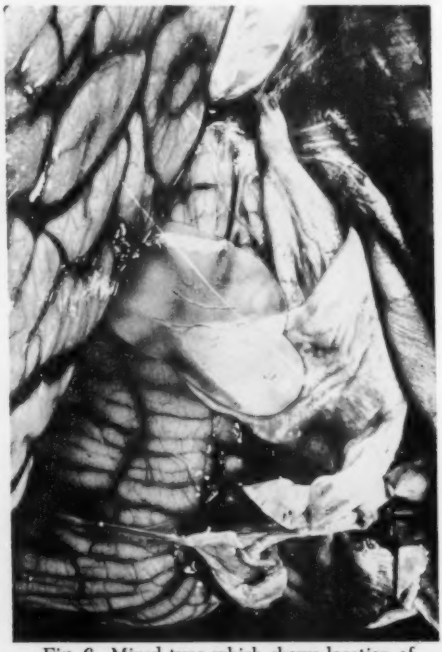

Fig. 6. Mixed type which shows location of parasite in the subarachnoid space

TABLE 1
SIGNS AND SYMPTOMS IN 31 CASES OF CEREBRAL CYSTICERCOSIS

Symptoms	
Headache	30
Vomiting	27
Impaired visual acuity	20
Blindness	4
Convulsions	7
Mental deterioration	5
Signs	
Papilledema	25
Optic atrophy	4
Foster-Kennedy syndrome	2
Visual field changes	7
Hemiparesis	18
Sensory disturbances	13

point of the obstruction. The results of these studies are as follows: In 18 of the cases, dilation of the ventricular system was revealed—12 symmetric and 6 asymmetric. Blockage of the ventricular system at different levels was present in 5 cases. In 4, the ventricular system and subarachnoid spaces were reported as normal.

Carotid arteriography was performed in 7 cases—4 unilateral and 3 bilateral. The findings were compatible with ventricular dilation. However, no other abnormalities were present.

3. Laboratory examinations. In 29 cases, the cerebrospinal fluid was examined. The samples were taken from the ventricular cavity and the lumbar subarachnoid space. We found changes compatible with the diagnosis of cerebral cysticercosis in 25 cases. The changes were an increase of cells (lymphocytic reaction), a decrease of sugar, an increase of proteins with positive Pandy reaction, a first zone colloidal gold curve, and a positive reaction to the cysticercosis (a complement-fixation test described by Dr. D. Nieto).[11–14]

TABLE 2
TYPES OF OPERATIONS USED IN TREATMENT OF CEREBRAL CYSTICERCOSIS

Operation	*Number of cases*
Bitemporal decompression	2
Exploration of posterior fossa and removal of cysticercus	5
Craniotomy with exploration of third ventricle and removal of cysticercus	2
Ventricular puncture with ventriculopleural anastomosis	8

TREATMENT

In general, the results of treatment for cysticercosis are not very satisfactory. All the different methods of therapy are as a rule palliative and seldom curative. The treatment depends upon the clinical type. In the parenchymatous types, corticosteroids have been used with the idea of avoiding the inflammatory reaction;[15] the results cannot be evaluated as yet. In the ventricular, subarachnoid, and mixed types, surgical procedures are indicated as palliative measures to decrease the intracranial pressure. The operations that were performed are listed in Table 2.

The results of these surgical procedures are difficult to evaluate at the present time. However, we should mention that 5 of the patients who were treated with ventriculopleural anastomosis died sometime after the procedure and showed signs of diffuse septic meningitis despite intensive antibiotic therapy.[16] Another 3 patients, who were not operated upon, died at the time of admission as a result of increased intracranial pressure. They represent a mortality rate of 26% under this limited observation. The 2 patients in whom a single cyst was removed from the third ventricle have had satisfactory results as far as the six-month follow-up.

CONCLUSIONS

1. Cerebral cysticercosis is a disease with a high incidence in Mexico.

2. The diagnosis of the disease in most cases is difficult due to the obscure clinical picture which often misleads the observer to think in terms of a cerebral tumor.

3. Cerebral cysticercosis is a seriously incapacitating disease with a high mortality rate.

4. The treatment, medical or surgical, is as a rule unsatisfactory, and only palliative measures are available at the present time.

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Spastic hemiplegia in man

Lack of flaccidity in lesion of pyramidal tract

W. Jann Brown, M.D., and Harry C. H. Fang, M.D.

RECENTLY, the functional significance of the pyramidal tract and the syndrome induced in man and animals by section of the pyramid has been discussed and reanalyzed.[1,2] New physiologic and anatomic technics have uncovered facts which have caused questions to arise in regard to the specificity and functional significance of this basic nervous structure. Opportunity for thorough study of so-called "pure" pyramidal lesions occurring naturally in the course of disease processes in man is very rare.

The human pyramids have been relatively inaccessible to the neurologic surgeon. Consequently, an attempt to evaluate the functional anatomy based on human material has failed. Autopsied cases most often show the complication introduced by involvement of neighboring neural structures.

This report is a study of the clinical characteristics of a patient and the anatomic details of an apparently isolated vascular lesion which interrupted the corticospinal tract at the pontomedullary juncture.

CASE REPORT

Clinical history. M.E.F., a 54-year-old man, was admitted to the Long Beach Naval Hospital on April 14, 1949, with a chief complaint of left-sided weakness. Twenty-four hours before, the patient suddenly felt his left leg weaken while walking toward his room. He continued to walk but then fell onto the bed. His speech was slurred. Prior to this episode, he had had some subjective loss of sensation in the arms and legs and a general feeling of weakness. No headache was noted.

Notable in the past history are the following facts. He was known to have had hypertension for thirty-two years. In 1939, he was hospitalized at the Brentwood Veterans' Administration Hospital, Los Angeles, for manic-depressive psychosis. In 1942, he was transferred to Veterans' Administration Hospital, Fort Sheridan, Wyoming, where he remained until 1943. On each of these admissions and discharges, neurologic examinations were reported as normal. Aside from hypertension, he was well between 1943 and 1949. The patient's father died at the age of 70 of "stroke." The grandfather and the patient's brother were said to have had manic-depressive psychosis.

Physical examination. The patient's blood pressure was 175/110 and the pulse was 80 per minute. The general physical state was not remarkable except for a systolic murmur at the apex. He was disoriented as to time, place, and person, and he talked constantly in a stream of irrelevant, disconnected thought. He was restless, agitated, and expressed many delusional ideas. Insight and judgment were impaired. The right pupil was larger than the left. Both pupils reacted to light and accommodation. Funduscopic examination revealed minimal sclerotic changes in the retinal arteries. The tongue deviated to the right on full protrusion. Gag reflex was present bilaterally. There was left facial weakness and flaccid paralysis of the left arm and leg. The arm was more affected than the leg. The patient could not move the fingers of the left hand nor was he able to make any gross movement of the proximal muscles of the left upper limb. He could make only a few weak movements of abduction of the left thigh. Tendon reflexes were brisk in the right arm and right leg and completely absent on the left. Left plantar response was extensor and right plantar response was flexor.

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Abdominal reflexes were absent bilaterally. Cremasteric reflex was present on the right side only. No disturbance in sensation was recorded. Lumbar puncture revealed an opening pressure of 152 mm. of water and closing pressure of 130 mm. of water; 10 cc. of spinal fluid was withdrawn. Study of the spinal fluid revealed no cells, 27.8 mg. per cent of protein, a negative colloidal gold curve, negative test for syphilis, and a 1+ Pandy reaction.

Clinical course. Two days following the onset of paralysis, weak minimal voluntary movements of the left leg were present. The left arm was motionless. Deep tendon reflexes were hypoactive in the left arm and left leg. Left extensor plantar reflex could be easily elicited. Speech was slurred. An electrocardiogram indicated an auricular rate of 78, with left axis deviation and left ventricular strain. Complete blood count, hematocrit reading, and blood urea nitrogen were all reported as normal.

Two weeks later the patient was more confused and talked continually, expressing many delusional ideas. He was transferred to the Brentwood Veterans' Administration Hospital. Examination on the day of transfer, April 28, 1949—two weeks after onset of symptoms—showed left hemiplegia; absent left abdominal, cremasteric, and achilles reflexes; and a left extensor plantar response. The facial weakness noted earlier disappeared, but the tongue still protruded to the right and speech was slurred. An electroencephalogram three weeks after initial onset of paralysis showed diffuse cortical abnormality.

There are few neurologic notes to indicate the subsequent course. However, eight months later, the patient could walk with a limp, but the left arm was weak and was held in flexion. After one year, during which he received physiotherapy, he could walk and get about with the use of a foot brace. Two years after the initial attack, slight wasting of the musculature in the left leg and arm with hyperactive reflexes and left extensor plantar response were recorded. The tongue still deviated to the right on protrusion.

During the five years following the initial onset of hemiplegia, the patient received 26 electroshock treatments without benefical effect on the psychotic reaction. He died suddenly while arguing with another patient.

Fig. 1. Gross photograph of ventral surface of lower brain stem. Arrow shows cystic area on right. Note uninvolved sixth nerve filaments traversing cyst.

Clinical diagnosis included chronic brain syndrome associated with cerebral arteriosclerosis; old thrombosis of the right middle cerebral artery with hemiplegia; and infarction of the myocardium.

Postmortem examination revealed a moderate degree of fibrous scarring and hypertrophy of the myocardium of the left ventricle. The liver was enlarged (2,000 gm.) and fatty. The gallbladder had been removed, and the common duct contained a few small calculi. Death was ascribed to acute myocardial ischemia associated with marked coronary arteriosclerosis.

Gross description of the nervous system. The undersurface of the dura was smooth and glistening. The venous sinuses and bridging veins were patent. The leptomeninges were moderately cloudy. The cerebral hemispheres were symmetrical and appeared normally developed. There was a mild narrowing of the gyri of the frontal and temporal lobes. The vessels of the base exhibited a moderate atherosclerosis, but multiple sectioning revealed no occlusion. In the midportion of the basilar artery, there was a small recent intramural hemorrhage. The cranial nerves were intact or appeared to be avulsed. There was a small sunken area 0.6 by 0.7 cm. in the tissue of the right pontomedullary juncture (Fig. 1). The right pyramid showed an extensive loss of its mass, and its upper anterior edge was covered by a patch of thickened leptomeninges. The brain, which was coronally sectioned, revealed a very slight enlargement of the ventricular system. Extensive sectioning revealed only an old small cyst 0.3 by 0.3 cm. in the head of the left caudate nucleus. The midbrain and upper and middle pons were not abnormal. At the level of the sixth nerve at a point where the corticospinal tracts converge to form the pyramid, there was a discrete malacic cyst measuring 0.4 by 0.4 cm. (Fig. 2). The cyst completely obliterated the origin of the right pyramid at the pons. The cerebellum showed no lesions. The medulla revealed atrophy of the right pyramid down to the level of the decussation. The spinal cord was not examined.

Microscopic description of the brain. Sections taken at 3 mm. intervals throughout the entire brain stem were studied in hematoxylin and eosin, Nissl, Bodian, Bielschowsky, and Weil preparations. These sections showed a mild general thickening of the pial vessels. The right pyramid was completely demyelinated (Figs. 3 and 4). The neuroglial nuclei in this tract were increased in number, and there was no evidence of active inflammation. The Bodian and Bielschowsky stained sections revealed a small number of scattered axis cylinders in the demyelinated atrophic pyramid (Fig. 5). The majority of these fibers were located near the internal arcuate fibers. A few of them were also seen in the pyramid in the vicinity of the external arcuate fiber bundle. The centrum of the pyramid contained only 9.7 fibers per square millimeter. The fibers were enumerated by use of the Whipple grid. Areas of the normal and involved pyramids were determined by the use of a compensating polar planimeter. The left pyramid measured 8.85 sq. mm. and contained a normal number of axis cylinders (Fig. 6). The area of the normal pyramid corrected for fixation shrinkage is 11.06 sq. mm. The involved pyramid measured 3.16 sq. mm. A simple calculation places the total number of surviving axis cylinders in the abnormal pyramid at 1,800. The latter figure includes fibers which were fairly close to the internal and external arcuate fibers.

A standardized ocular micrometer was used to measure 100 of the axis cylinders, and 65% of these fibers measured 1 to 4 $m\mu$. in diameter and 33% measured 5 to 10 $m\mu$. No fibers larger than 11 $m\mu$. were noted. The fiber

Fig. 2. Section through hindbrain showing small cystic cavity in corticospinal tract at lower end of pons. × 4

Fig. 3. Section is made through medulla at juncture with pons and sloped somewhat, giving the longitudinal aspect of the corticospinal tract. Uninvolved tract is on left. Weil stain. × 35

Fig. 4. Showing demyelinization of right pyramid at midolive level. Note lack of involvement of paramedian structures. Weil stain. × 6

counts and areas were measured in a section of the medulla just above the decussation of the pyramids. The vessels were generally thickened, but, in the vicinity of the cyst, the paramedian branches were nonetheless patent. The Weil preparations revealed no loss of the myelin sheaths of the medial lemniscus, arcuate fibers, medial longitudinal fasciculus, olivocerebellar fibers, tracts of the reticular formation, or tectospinal tracts. Holzer, Gomori trichrome, and PTAH stains revealed no abnormal collection of neuroglial nuclei and fibers in the reticular formation or in the tracts surrounding the demyelinated pyramid. The neurons of the inferior and accessory olives, reticular formation, and cranial nerve nuclei did not appear diminished in number or altered in contour. In a section of the brain stem just above the region of transition from medulla to pons, where the fasciculi comprising the pyramid are embedded in the pons, the lesion abruptly ended (Fig. 7). Here intermixed glial fibers and a microcyst have replaced the area formerly occupied by the pyramidal bundles. The edges of the cyst have encroached minimally upon the surrounding pontine nuclei and associated pontine strata. The nuclei of the sixth, seventh, and eighth nerves were intact as were the respective tracts. The tracts of the right twelfth nerve appeared to contain fewer fibers than the left tracts. The neurons of the nearby pontine nuclei contained normal amounts of Nissl substance. A small patch of demyelinization was found in the brachium pontis on the side of the lesion, but this appeared to be a much more recent lesion (Fig. 7). Occasional gitter cells were seen at the edge of the cyst at some levels. There was no unusual number of neuroglial cells across the median raphé. Figure 8 shows a section of pons at the level of the seventh nerve exit; loss of myelin and gliosis may be seen in the upper portion of the pyramidal tract. A Weil preparation of a more rostral portion of the pons revealed a slight diminution of myelin in the right corticospinal tracts. The Bodian and Bielschowsky preparations revealed axis cylinders of all calibers in these tracts. The substantia nigra appeared normal on both sides. The corticospinal segment of the peduncle on the uninvolved side contained large, small, and inter-

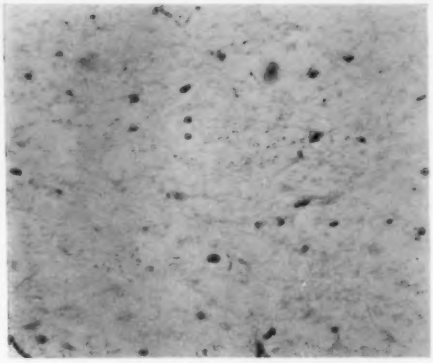

Fig. 5. Photomicrograph of atrophic right pyramid. There is a lack of axis cylinders. Dark structures are neuroglial nuclei. Bielschowsky preparation. × 270

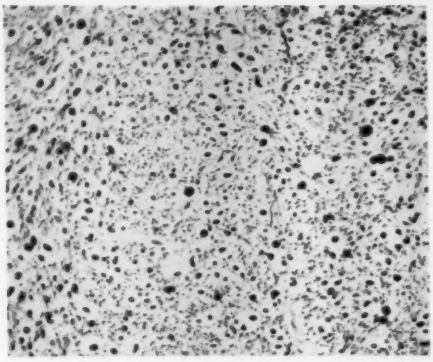

Fig. 6. Photomicrograph of left pyramid which displays normal distribution of the axis cylinders. Bielschowsky preparation. × 270

mediate sized fibers. On the right, however, there was a slight sparsity of the myelin in the middle third and a slight decrease in the number of the larger fibers, but the greater number were still present. The right internal capsule posterior to the genu contained less myelin than that of the left side. The precentral gyrus was serially sectioned bilaterally but in a direction parallel to the rolandic fissure. When taken together, there was a marked decrease in the pyramidal cells of laminae III and V on the right. Detailed cell counts were not made. Some large pyramidal cells were noted on the involved side, especially in the face area. Sections of areas 3, 1, and 2 on the right showed some cell loss and an increase in neuroglial cells.

Description of the remainder of the central nervous system. In the cerebellum, there was a slight decrease in the Purkinje cells. A few of the neurons of the dentate, emboliform, globose, and fastigial nuclei were shrunken and the surrounding neuroglial nuclei were increased.

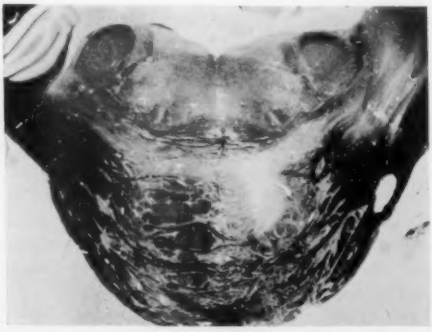

Fig. 7. Section of pons below seventh nerve level and just above transition from medulla to pons to show rostral extent of cyst. Note also area of recent demyelinization in brachium pontis. Weil stain. × 3

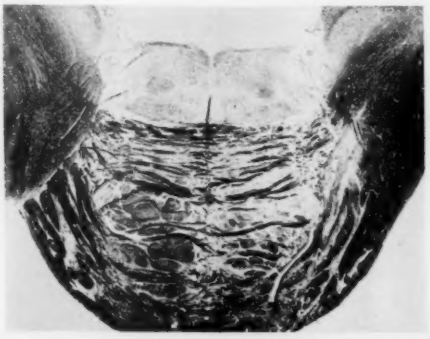

Fig. 8. Section of pons just above area shown in Figure 5. Note structures of pons are intact with exception of demyelinization of parts of corticospinal tract on right side. Weil stain. × 3

There was some neuron loss in different layers of the right and left frontal cortex in areas 10, 8, 6, and 44, but this was minimal.

Bilateral sections of the occipital lobe (area 17) and superior temporal gyrus revealed no abnormalities.

The pyramidal cells of the hippocampus were not decreased on either side.

Sections of thalamus, globus pallidus, caudate nucleus, and putamen showed some enlargement of perivascular spaces bilaterally but no apparent decrease in the number of neurons.

DISCUSSION

Pathologically, a sharply localized infarct was found which involved the corticospinal bundle at the right pontomedullary juncture. The infarction spared the medial lemniscus, medial longitudinal fasciculus, tectospinal tract, olivary nuclei, and tracts and cranial nerves and their respective nuclei. The small malacic cyst was probably the result of an occlusion of a paramedian branch of the basilar artery. Serial sections of the involved portion of the medulla, pons, and mesencephalon, however, revealed neither occluded vessel nor organized clot, although all vessels showed marked thickening of their walls. The occurrence of a few gitter cells at the edges of the lesion intermeshed with some fibrous and glial tissue may have indicated a more recent minimal extension of the lesion, but, in the main, the cyst appeared old.

Below the lesion, large, small, and intermediate sized axis cylinders as well as myelin sheaths, of course, were lost. A count of the fibers in the uninvolved side revealed 867,000 axis cylinders in the pyramid above the decussation. The damaged corticospinal tract on the right contained 1,800 fibers. The fiber counts of 867,000 and the area of 11.06 sq. mm. of the normal pyramid correspond with values in the literature.[2]

Axis cylinders of the large type were decreased above the lesion on the involved side up to the level of the upper pons but were present at all levels above.

The region of the internal capsule posterior to the corticospinal tract was not extensively examined except in coronal sections, hence any comparison of one side with the other and evaluation of a possible ascending system in this area as postulated by Nathan and Smith[3] was not possible. Although the lesion in this case was approximately five years old, it was decided to do Marchi preparations above and below the lesion to determine the extent of any recent ascending or retrograde degeneration. The preparations, however, revealed no recent demyelinization nor any osmic acid stained material trapped in the few enmeshed gitter cells.

The axis cylinders of the corticobulbar radiation in the internal capsule appeared to be fairly equal in number and size.

The pyramidal cells of laminae III and V were largely lost from the precentral gyrus on the right side, although the related axis cylinders on this side did not appear to be decreased.

The state of preservation of the axis cylinders above the lesion in this case is similar to the findings of others. In cases of thrombosis of the anterior spinal artery in man located at the medullary level, Davison[4] found that pyramidal fiber degeneration proximal to the complete demyelinization of the pyramid in the lesion did not even reach the pontine level where the fibers were found to be intact. Schröder[5] studied human cases having lesions of cord and medulla and found loss of pyramidal cells but no loss of fibers above the lesion. Initially, we believed that loss of fibers had occurred above the lesion, but this has since been shown to be an artifact introduced during gold toning of the Bodian and Bielschowsky preparations.

A survey of the literature reveals no comparable verified lesion confined to this portion of the corticospinal tract in man. A surgical placement of such a circumscribed lesion has not been reported to our knowledge. The cases reported by Davison[4] are not comparable because they were lower in the medulla and involved not only the corticospinal tracts but the medial lemniscus, tectospinal tract, and medial longitudinal fasciculus with partial demyelinization of the parolivary and hilar fibers of the inferior olivary nucleus. Davison's cases further showed myelin loss and atrophy in the restiform body, and, in another case reported by him, there was demyelinization of both pyramids at the level of the tenth nerve nu-

cleus as well as of the left medial lemniscus, tectospinal tract, and posterior longitudinal bundle; partial destruction of vestibular nucleus medialis, corpus restiform, and part of the nucleus and tractus solitarius on one side and many other lesions in the cerebrum.

The deviation of the tongue to the side of the lesion is explained in our case by probable involvement of emergent fibers of the left twelfth nerve. The fibers were decreased within the medulla on the involved side.

Hausman[6] reported a case with flaccid hemiplegia and no sensory defect. There was, however, no anatomic confirmation that the lesion was confined to the pyramid. A later communication with Dr. Hausman[7] revealed that contact with this patient has since been lost.

Failure to find degeneration of axis cylinders above lesions in these portions of the descending motor pathway may be partially explained by the existence of the motor collaterals described by Cajal.[8] These collaterals are numerous in areas in which the pyramidal tract is in contact with the reticular substance, especially at points above the olives at the level of the seventh nerve nucleus. At these points, the collaterals occur at right angles and pass dorsally as isolated fibers or as small fasciculi and disperse in the anterior half of the reticular substance. The longitudinal extension of these collateral connections has not been fully explored, but that such motor neurons and interconnections do exist between bulbar nuclei and pyramidal tract is well known.

Vascular disease in the central nervous system is unique in that it often provides valuable information for understanding functional localization. When vascular disease causes isolated and circumscribed lesions in certain neural structures, the mechanisms served by such structures may be even more sharply defined. Our case points out the need for analysis of comparable material in this regard.

CONCLUSION

A clinical account and detailed pathoanatomic study of initially flaccid (later found spastic) hemiplegia with crossed hypoglossal paralysis arising from a unilateral focal infarction of the medullary pyramid involving emergent fibers of the hypoglossal nerve in man has been presented. Pertinent literature regarding certain aspects of the human pyramidal tract has been reviewed, and the need for further analysis of comparable material is stressed.

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Temporary bilateral occlusion of the common carotid and vertebral arteries in the monkey at normal body temperature

David E. Donald, B.V.S., M.R.C.V.S., Ph.D.,

and Robert J. White, M.D.

EXPERIMENTAL AND CLINICAL OBSERVATIONS of Sealy and associates[1] and Sweet and Koons[2] have indicated that temporary interruption of arterial inflow to the brain may be carried out without untoward results, provided cerebral metabolism has been sufficiently reduced by general or local hypothermia. The complex network of connections between arteries supplying the brain and the number of anastomoses with adjacent vessels render it difficult to obtain complete interruption of arterial inflow to the brain by vascular occlusion. Thus, in experimental studies, the degree of protection afforded by hypothermia during a period of cerebral-inflow stasis generally is measured against the results of a similarly produced period of inflow stasis at normal body temperature. It is well recognized, as Cooper[3] and Andreyev[4] have shown, that some 50 to 60% of dogs will survive bilateral occlusion of common carotid and vertebral arteries and that 40% of the survivors will exhibit no neurologic sequelae.

The high level of cerebral development in the monkey makes this animal eminently suited to neurologic evaluation in studies of interruption of arterial inflow to the brain during hypothermia. Hill[5] stated that ligation of both carotid arteries and one vertebral artery was almost always fatal in the monkey. Gardner[6] found no permanent neurologic deficits in monkeys after simultaneous unilateral ligation of the vertebral, common carotid, and internal and external carotid arteries. However, after ligation of the major cervical vessels on one side, ligation of the common carotid artery on the other side resulted in the death of 2 of 3 monkeys, even when the second ligation was done nine to twelve months after the first. Information regarding the results of temporary bilateral occlusion of the common carotid and vertebral arteries at normal body temperature was not readily available, and it was to gain data of this type that the following studies were carried out. The series, although small, indicates that in the monkey, as in the dog, bilateral occlusion of the common carotid and vertebral arteries for thirty minutes at normal body temperature is not invariably fatal or always accompanied by signs of cerebral dysfunction.

METHODS

Ether was used to lightly anesthetize 5 Rhesus monkeys weighing 4.8 to 8 kg. to permit their being placed in a restraining chair. On recovery from the effects of the ether anesthesia, the animals were anesthetized by the intravenous administration of a solution containing 20 mg. of pentobarbital sodium per cubic centimeter and were placed in the supine position. A flexible cuffed endotracheal tube was inserted. Respirations were monitored throughout by means of a thermocouple placed in the endotracheal tube. Systemic arterial and central venous pressures were measured by strain gauges attached to catheters placed in the abdominal aorta and inferior vena cava via ex-

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Prepared with the technical assistance of David Ferguson.

posed femoral vessels. Electrocardiographic leads were attached to both forearms and the left hind limb.

The common carotid and vertebral arteries were exposed through bilateral incisions extending from the level of the clavicle to the larynx. The common carotid artery was isolated at its bifurcation, and the carotid branches were identified. Blunt dissection between the bundles of the longus colli muscle exposed the vertebral artery and vein as they approached the transverse process of the sixth cervical vertebra. Snare ligatures were passed around the arteries and were then led through short lengths of glass tubing, the tips of which had been narrowed to fit snugly about the ligatures. Occlusion of the artery was produced by traction on the ligature until the vessel was firmly compressed against the tip of the glass tubing. Occlusion of the arteries was completed within one minute and maintained for thirty minutes when the snares were released and the ligatures withdrawn. The muscles of the neck were apposed with a few catgut sutures, and the skin incisions were closed with interrupted silk sutures. For two days postoperatively, 500,000 units of penicillin was given intramuscularly.

It should be noted that the animals did not receive heparin before the vascular occlusion.

RESULTS

All 5 animals survived the period of vascular occlusion. In the postoperative period, 2 animals gave evidence of severe cerebral damage. In 1 animal, the damage was overwhelming, and the animal led a "vegetable" existence until it died on the fourth postoperative day. A second animal suffered severe impairment of motor and postural reflexes, being incoordinated in movement and unable to maintain the sitting posture. The animal was apathetic and showed little or no resistance to handling. Although able to chew and to swallow when food was placed in the mouth, the animal would not feed itself, even when the food was placed in its paw. Tube feeding was continued for fourteen days postoperatively, at the end of which the animal commenced to feed itself by picking food directly off the floor of the cage with its mouth. Further improvement was shown during the next two weeks and the animal became freely ambulatory, although some degree of weakness remained on the left side. Initially, only the right paw was used in feeding. Ultimately, both paws were employed. The animal was much less aggressive than in the preoperative period.

Of the 3 animals which recovered completely, 2 regained full activity by the second postoperative hour. In the third animal, recovery was slower, and the animal did not become ambulatory until the fifth to sixth postoperative hour, at which time there was still some uncertainty in balancing. At the end of twelve hours postoperatively, this animal was normal in all respects. In order of operation, the first and second animals showed complete recovery, the third animal died on the fourth postoperative day, the fourth was severely damaged cerebrally, although ultimately able to maintain itself without special care, and the fifth and final animal obtained complete recovery.

All animals exhibited cardiac acceleration and moderate to marked systemic arterial hypertension during the period of occlusion. In 2 of the 3 animals which recovered completely, moderate to marked ectopic activity was recorded in the electrocardiogram throughout the period of occlusion, with disappearance of the cardiac irregularity on release of the ligatures. Respirations became slower and more shallow in the 2 animals which showed cerebral damage, while, in the other 3, there was either no change or a slight increase in rate.

SUMMARY AND CONCLUSIONS

As Kaupp and associates[7] have shown, the brain deprived of arterial inflow suffers irreversible damage if the cessation of flow is continued for more than twelve to thirteen minutes. Complete recovery of the 3 animals indicated that in these cases, despite occlusion in the neck of the 4 major vessels to the brain, sufficient blood entered via collateral channels to maintain the integrity of the brain substance. In the other 2 animals, occlusion of the 4 major vessels effectively deprived the brain of arterial inflow and resulted in severe cerebral damage sufficient in 1 case to cause the death of the animal. A sixth animal was available for acute experimentation. The common carotid and vertebral arteries were occluded in the usual manner. After eighteen minutes, the

animal was exsanguinated and injected with a barium-gelatin mixture via a cannula placed in the descending aorta and administered at an injection pressure of 200 mm. Hg. Subsequent dissection proved the completeness of occlusion at the ligature sites but revealed a well-filled cerebral arterial system. The principal collateral pathways appeared to be branches of the costocervical, omocervical, and intercostal arteries.

Although the series is small, the results clearly show that bilateral occlusion of the common carotid and vertebral arteries in the monkey cannot be relied upon to interrupt completely arterial inflow to the brain. The complete recovery of 3 of 5 animals in which thirty minutes of occlusion was maintained at normal body temperature suggests that, if this type of occlusion is carried out under hypothermic conditions, caution must be exercised in interpretation of the results.

The 3 main points may be given briefly: [1] A group of 5 Rhesus monkeys underwent bilateral occlusion of the common carotid and vertebral arteries in the neck for a period of thirty minutes at normal body temperature, and this was followed by complete recovery of 3. [2] Severe cerebral damage was manifested in the postocclusion period by 2 animals; in 1, this damage was sufficient to cause death. [3] The principal collateral sources whereby blood bypassed the occluded vessels were branches of the omocervical, costocervical, and intercostal arteries.

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Karl Gunnar Vilhelm Wohlfart

March 9, 1910–March 23, 1961

THE UNTIMELY DEATH of Professor Wohlfart on March 23, 1961, came as a shock to his many friends in Europe and the United States. The combination of a superior clinician, teacher, and research worker is rare enough, but when to this are added outstanding personal qualities, a rich cultural background, and great abilities of leadership, the true stature of Gunnar Wohlfart becomes apparent.

Wohlfart was born and raised in Stockholm. His parents were the composer, Karl Wohlfart, and his wife, Erin Westrin. He studied medicine at the Karolinska Institutet in Stockholm, obtaining the licentiate of medicine in 1936 and his doctorate degree in 1937. His thesis, "Über das Vorkommen verschiedener Arten von Muskelfasern in der Skelettmuskulatur des Menschen und einiger Säugetiere," presaged his continuing interest in muscle diseases for which he later was to become so well known.

He served as a docent (assistant professor) in histology from 1937 to 1943 and at the same time obtained further graduate training in medicine and in neurology (1939 to 1944) at the Serafimerlasarettet in Stockholm under Professor Nils Antoni. He was docent in neurology from 1943 to 1950 and in periods from 1945 to 1949 served as temporary head of the Department of Neurology at the Serafimerlasarettet. Additional training in psychiatry and occupational medicine as well as travel for purposes of study in The Netherlands, Germany, Austria, Yugoslavia, France, and the United States were crowded into this busy fourteen-year period of postgraduate preparation.

When in 1950 he was made Professor of Neurology at Lund (the first to hold this chair), he had been adjudged competent for faculty appointments in 5 different dissertations. He in turn served as an expert in the appointments of 3 professors of neurology (Oslo, 1954; Uppsala, 1958; and Umeå, 1959) and 1 professor of neurosurgery (Lund, 1961). He was a member of several societies, including honorary membership in the Philadelphia Neurological Society, honorary-corresponding membership in the American Academy of Neurology, and corresponding membership in the American Neurological Association. He served as Visiting Professor of Neurology at the University of California School of Medicine, San Francisco, in 1950 and again in 1957.

Wohlfart's interest in research was intense and sustained, as can be seen from his bibliography which contained 90 titles. More than half of his contributions involved pathologic or experimental studies, and the remainder were of a clinical nature. His histopathologic studies on the diseases of muscle were particularly illuminating and have contributed greatly to our basic knowledge in this field. His extensive background of training in histopathology and neurology contributed to make him one of the foremost authorities in the world on motor neuron and primary muscle diseases. It was typical of his progressive attitude that 2 of his last publications in 1960 concerned studies on the degeneration and regeneration of peripheral nerves with the use of the electron microscope.

An interesting sidelight on his research abilities concerned his studies on "Gengas" during World War II. "Gengas" was used in Sweden as a wartime substitute for gasoline and was obtained by burning pretreated wood in a special container placed on cars. This wood also produced carbon monoxide, and it was thought by many doctors that prolonged exposure to low concentrations of this toxic gas might produce such symptoms as fatigue, headache, and irritability. This was considered a great public health problem at the time, and

taxi drivers and other exposed drivers, when they complained of the symptoms mentioned, were looked upon as victims of this toxic condition. The condition was considered an occupational disease, and a project at the Karolinska Sjukhuset was devoted to the study and care of such patients. In 1945-46, Wohlfart was assigned to the Gengasavdelningen, and it was due to his work that the problem was solved and that the taxi drivers of Stockholm were again put back to work.

In his eleven years at Lund, he had established an outstanding department of neurology with strong developments along both clinical and research lines. He had organized a laboratory of neuroanatomy and took special interest in the training of his graduate students in research. He had started a subdivision of occupational medicine, which later developed into a separate department. During his last years, he had contributed greatly to the planning of a department of rehabilitation, integrating to this end the interests of such ancillary groups as orthopedic surgeons, rheumatologists, physical therapists, and psychiatrists.

Beyond all his accomplishments as a neurologist, teacher, and investigator, Wohlfart possessed strong cultural interests in art and music and took a lively interest in all aspects of the social and political life of his times. Perhaps his most outstanding qualities were his emotional stability and his intellectual integrity. Behind his outer facade of Swedish formality was a depth of understanding and warm friendship which was prized highly by all who knew him well. His friends, colleagues, and indeed the entire neurologic world will share with his wife, Gun, and his immediate family their keen sense of personal loss.

ROBERT B. AIRD, M.D.

Neurology

BOOK REVIEWS

A Functional Approach to Neuroanatomy

by Earl Lawrence House, Ph.D., and Ben Pansky, Ph.D., 494 pp., ill., Blakiston Co., New York City, 1960. $12.50.

This generously illustrated neuroanatomic text was written, as pointed out in the preface, with the needs of medical students uppermost in mind. The plan of the book is straightforward and in keeping with its purpose. In the first 6 chapters, the evolution, gross anatomy, vasculature and meningeal investments, development, and histology of the nervous system are discussed. The following chapter presents the functional classification of afferent and efferent systems into nerve components; the chapter includes a useful classification of reflexes in terms of their afferent and efferent limbs. The next 10 chapters cover the afferent and efferent systems in detail. The final 6 chapters are concerned with the cerebellum, extrapyramidal and pyramidal systems, hypothalamus, thalamus, and cerebrum. Reports of 18 clinical cases, an atlas of brain stem sections in transverse and coronal planes (from Villiger), and a list of references complete the volume. The illustrations, which are the work of Dr. Pansky, are lucid, closely related to the text, and well planned in their sequence. Adaptations of illustrations by others, as for example, the pictures of Netter on the hypothalamus, are included because of their obvious didactic value. Some diagrams, such as those on the external morphogenesis of the brain, may strike some readers as too schematic. In this instance, as well as in the series of illustrations of gross external and internal features of the brain, one wishes that an occasional half-tone had been included to complement the more schematic representations. Balanced against this criticism is the fact that the authors present internal topography early in the book with emphasis on relation to surface features. This will be appreciated by instructors. The text is concise and well-organized, with abundant clinical illustrations and a strong functional emphasis throughout. On the whole, the book appears well suited for use in a basic neuroanatomy course.

J.B.A.

Neurovascular Compression Syndromes of the Shoulder Girdle

by Louis M. Rosati, M.D., and Jere W. Lord, M.D., 168 pp., ill., Grune & Stratton, New York City, 1961. $7.25.

The subject of this book concerns all conditions involving mechanical pressure or angulation of the subclavian vessels and brachial plexus from the thoracic inlet or superior aperture of the thorax to the midaxilla or region of the insertion of the pectoralis minor muscle into the coracoid process. These conditions have usually been considered under 1 of 5 syndromes—the cervical rib, the scalenus anticus, the costoclavicular, the hyperabduction, and scalenus medius. Often, these conditions are combined, 2 or even 3 being responsible for the clinical picture. In this little volume, Drs. Rosati and Lord describe the anatomic features of the retroclavicular region which predispose to compressive syndromes. After chapters on the anatomy of the region, the pathophysiology of osseous, muscular, and tendinous structures which may impinge on nerves and vessels is described. The clinical symptoms, diagnostic tests, and differential diagnosis are presented and illustrated by short case reports.

Finally, the therapy—both conservative and operative—is described for each condition. A tabulation is given of the history and findings in 51 patients with neurovascular compression. References to the American and English literature on the subject and an adequate index are appended.

In general, the clinical parts of the book are excellent and well illustrated by beautiful drawings by Netter. The diagrammatic line sketches of anatomic features, while less pleasing to the eye, are instructive. A few roentgenograms add clarity. Some discussion of the technical neurologic and vascular studies such as electromyography and oscillography, which are of considerable value in the diagnosis of these conditions, would have made the coverage of the subject more complete. However, it is an excellent clinical summary of a controversial subject which should be familiar to neurologists, neurosurgeons, and general surgeons.

A.E.W.

Neurological and Neurosurgical Nursing

by C. G. de Gutierrez-Mahoney and Esta Carini, third edition, 413 pp., ill., C. V. Mosby Co., St. Louis, 1960. $6.50.

This book covers in considerable detail the nursing procedures required for the care of patients with a broad spectrum of neurologic and neurosurgical disorders. In addition, it attempts to furnish sufficient background about the disorders to assist the nurse toward an informed approach to her task.

The early chapters lay an historical and neuroanatomic background for subsequent subjects. Following chapters are devoted to specific descriptions of a large number of diagnostic and treatment procedures which are used in neurology and neurosurgery. A small representative sample of the procedures may be mentioned here for illustrative purposes: neurologic examination, electroencephalogram, spinal puncture, nerve block, nasal feeding, use of a respirator, and eye care. Informative background is given for each procedure and followed by detailed instructions concerning equipment required, the preparation of the patient, the procedure itself, aftercare of the patient, and aftercare of the equipment.

Most of the remainder of the book deals with specific neurologic and neurosurgical conditions. The following serve as an illustrative sample of some of the subjects covered: the unconscious patient, convulsive disorder, degenerative disease, intracranial tumor, and injury. In each instance, a concise description of the disease is followed by details of nursing observation, procedures, equipment, and care appropriate to the condition.

Much emphasis in this book is placed on surgical therapy and upon nursing procedures related to surgical conditions. Comparatively less attention is given to the role of the nurse in the medical and rehabilitative care of the patient. One might wish that some of the subject material and some of the chapters on medical neurologic conditions were organized in a different manner. Despite these criticisms, this is an excellent book which is clear, concise, and specific.

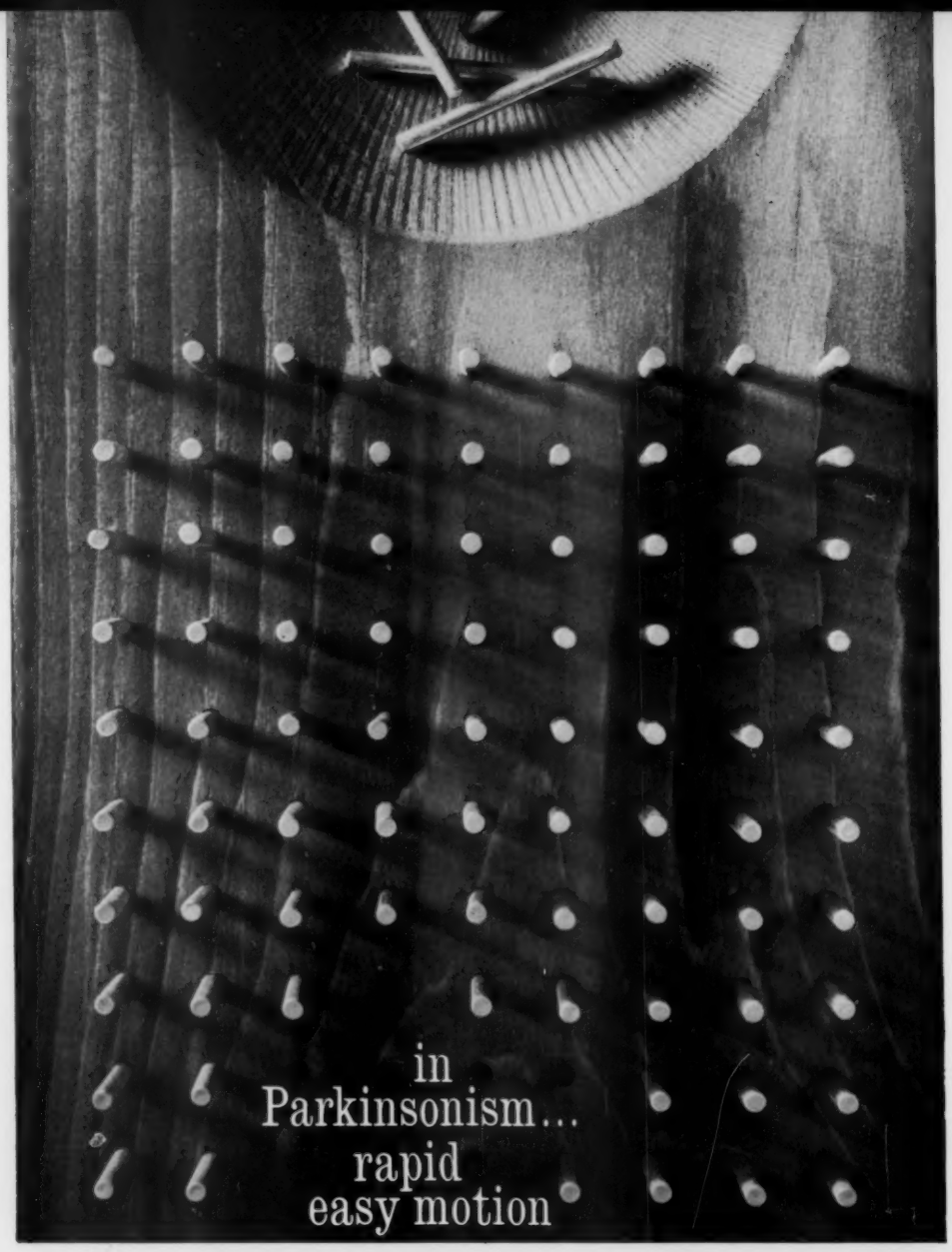
J.R.B.

Kernicterus and Its Importance in Cerebral Palsy

a conference presented by the American Academy for Cerebral Palsy, 306 pp., ill., Charles C Thomas, Springfield, Ill., 1961. $8.75.

Unfortunately, as is explained in the preface, there has been considerable delay in the publication of the proceedings of this conference. The first 2 presentations relate to the biochemistry of hyperbilirubinemia. These are brief and well done. However, since the papers were presented, a great deal more work has been done in this field. The bulk of the volume is taken up with an excellent presentation of the pathology as studied in 80 cases of kernicterus and 7 cases of posticteric encephalopathy. This is a very complete presentation. Attached to the book is a table giving the clinical and autopsy data on the 80 cases. The bibliography is most complete. This is followed by an interesting chapter on the auditory deficits in the kernicteric child. The concluding chapters are on the clinical problems. The section on pathology is highly recommended. It will serve as a standard reference on the problem for a long time.

J.P.R.



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(1) Carter, S.: *M. Clin. North America* 37:315, 1953.
(2) Maltby, G. L.: *J. Maine M. A.* 48:257, 1957.
(3) Buchthal, F.; Svensmark, O., & Schiller, P. J.: *Arch. Neurol.* 2:624, 1960.

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

SEPTEMBER 1961

Augustus S. Rose, M.D., President
A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
Robert Utterback, M.D., Secretary
Charles M. Poser, M.D., Treasurer

Request from the American Board Executive Secretary-Treasurer David A. Boyd, Jr., requests that all diplomates of the American Board of Psychiatry and Neurology assist in maintaining their current mailing addresses and professional appointments on file in the Executive Office of the Board. In the event of any change of address or professional appointment since the date of certification, each diplomate concerned should forward this information to the American Board of Psychiatry and Neurology, Inc., 102-110 Second Avenue, N.W., Rochester, Minn.... Such data, Dr. Boyd explains, is essential in order to maintain an up-to-date address file on all Board diplomates in view of the ever-increasing number of inquiries addressed to the Board. Cooperation from all diplomates would be appreciated.

Neuropathologists Elect Cowen President The American Association of Neuropathologists at their thirty-sixth annual meeting June 12, 1961, in Atlantic City elected David Cowen of New York as new President of the Association, Leon Roizen (New York) as President-Elect, and Angel Pentschew (Baltimore), Irwin H. Feigin (New York), and Humberto Cravioto (Mexico City) as Vice-President, Secretary-Treasurer, and Assistant Secretary-Treasurer, respectively.

Harvey Cushing Society Elects New Officers At the 1961 meeting of the Harvey Cushing Society held in Mexico City April 17 through 19, 1961, Leonard T. Furlow (St. Louis) was elected President; David L. Reeves (Santa Barbara), President-Elect; Joseph P. Evans (Chicago), Vice-President; Henry J. Svien (Rochester, Minn.), Secretary; Eben Alexander, Jr. (Winston-Salem), Treasurer; and Louise Eisenhardt (New Haven), Historian. The next Harvey Cushing meeting will be held in Chicago, April 30 through May 2, 1962.

Henry New President of EEG Society At the 1961 meeting of the American Encephalographic Society, Charles E. Henry was elected President. The other 1961 officers are Cosimo Ajmone-Marsan (Bethesda), President-Elect; Kenneth A. Kooi (University of Michigan Medical Center, Ann Arbor), Secretary; and Isadore S. Zfass, Treasurer.

Chambers Takes Neurology Chair Dean James E. McCormack of the Seton Hall College of Medicine in Jersey City has announced the appointment of Richard A. Chambers as the next Professor of Neurology and Director of the Division of Neurology at Seton Hall, succeeding Joseph M. Foley who has assumed the Chair of Neurology at Western Reserve University School of Medicine in Cleveland. Dr. Chambers was born and medically trained in England. Since 1949, he has been a member of the Royal College of Physicians, London. Twice he came to this country as a research fellow in neurology at the Boston City Hospital, the first time in 1951, later in 1956. Dr. Chambers went to Canada in 1957 where he was assistant physician in neurology at Toronto General Hospital. He also was clinical teacher in neurology and associate in neuropathology at the University of Toronto Medical School. He was appointed Assistant Professor of Neurology at Seton Hall College of Medicine in 1960.

National Leaders Speak at Neuropathology Symposium Leading national authorities in neuropathology and related fields served as a faculty at the unique teaching symposium at the University of Vermont, June 25. Purpose was to stimulate young investigators to pursue research careers in neuropathology. The Symposium was organized by the Pathology Study Section of the National Institutes of Health and supported by a grant of the NINDB in cooperation with the New England Deaconess Hospital. Some 150 young investigators now training in neurology, pathology, and neurobiology attended the Symposium. Many presentations dealt with molecular and cellular approaches to diseased and healthy neural tissues; others were concerned with neuroembryology, concepts of mental disease, experimental demyelinating diseases, vascular disease, neurotoxins, epidemiology, and the effects of radiation on the nervous system. The Symposium was chaired by Samuel P. Hicks of Harvard Medical School and the New England Deaconess Hospital. Among the outstanding contributors were Sarah A. Luse, Eli Robins, and Rita Lavi-Montalcini. Also participating were speakers from Israel and Great Britain. The summation was made by Harry M. Zimmerman.

Moore Receives NNRF Award The Scientific Committee of the National Neurological Research Foundation announces that John Wilson Moore has been awarded an NNRF fellowship. Dr. Moore became Associate Professor and Chief of the Division of Cellular Neurophysiology in the Department of Physiology at Duke University School of Medicine. The members of the Scientific Committee who make these fellowship awards are R. D. Adams, Chairman; Edwin W. Dempsey; Louis S. Goodman; Seymour S. Kety; Oliver Lowry; Horace W. Magoun; James L. O'Leary; and A. Earl

Walker....Foundation fellowships carry a stipend of $12,000 per annum for five years to conduct basic research on disorders of the central nervous system. The Foundation is now processing applications to be voted by the Scientific Committee at their next meeting at the time of the annual meeting of the Association of Research in Nervous and Mental Diseases in December 1961. All applications and pertinent information should be received before November 1, 1961. For further information, contact the National Neurological Research Foundation, 3255 N Street, N.W., Washington 7, D.C.

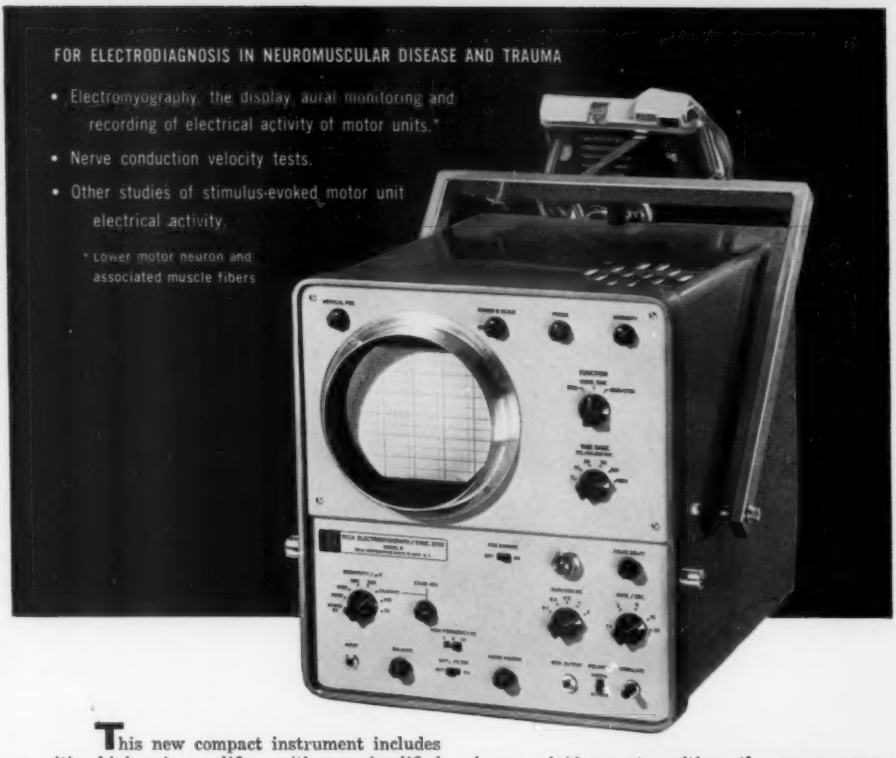
Stereotactic Surgeons To Meet in Philadelphia October 14 through 20, 1961, a group of international authorities will convene in Philadelphia for a symposium on stereoencephalotomy, which has been organized by the Cerebral Stereotactic Institute of Temple University under the direction of E. A. Spiegel and Henry T. Wycis. The program will include a presentation on the many phases of stereotaxic surgery by well-known international authorities and a discussion of extrapyramidal disorders. In addition, there will be an exhibit of stereotaxic apparatus. Inquiries should be sent to Dr. Henry T. Wycis, 3401 N. Broad Street, Philadelphia 40.

Here and There Dr. Benjamin Pasamanick, Professor of Psychiatry at the Ohio State University and Director of Research at the Columbus Psychiatry Institute and Hospital, has been named the Percival Bailey Lecturer for 1961. He will speak on "Some Misconceptions Concerning Racial Differences in the Prevalence of Mental Disease" at the Illinois State Psychiatric Institute in November 1961....The Third International Meeting of Neurobiologists will be held at the Anatomical Institute of the University of Kiel, Germany, in September 1962. The Honorary President of the Symposium will be Elisabeth C. Crosby of Ann Arbor. The topics selected for discussion are the Rhinencephalon, Hypothalamus, and Chemical Specificity of Some Neuronal Systems. Chairman of the Local Committee is W. Bargmann, Neue Universität Olshausenstrasse 40/60, Kiel, Germany....Frederick Andermann, President of the Fellows' Society, announces the existence of an annual lectureship at the Montreal Neurological Institute, known as the Fellows' Society Annual Lecture. The lecturers are chosen from senior (past) fellows of the Institute and are presented to fellows, visiting senior fellows, staff, and guests. Previous lecturers were Joseph Evans, Dorothy Russell, Webb Haymaker, and Isadore Tarlov. The Fifth Annual Fellows' Lecture was delivered June 7 by Guy L. Odom, who spoke on vascular lesions of the spinal cord.

Newsletter Reporter Resigns

Your reporter, because of overburdening commitments, regrets he can no longer write the AAN Newsletter. This issue will be his last.... Some twelve years ago, this AAN Newsletter first saw the light of day. It was just before the annual Academy meeting at French Lick Springs in 1948. Those were early rough-and-tumble days when our nascent Academy was seeking identity under the drive of its first president, A. B. Baker. Then the Newsletter consisted only of mimeographed sheets which were mailed to its small membership. Later, in 1952, when NEUROLOGY appeared as the official AAN journal, the Newsletter became part of the journal's monthly output. During the extraordinary and rapid growth of the Academy, the Newsletter has endeavored to depict the events in a way that may provide the skeleton for a living history of the Academy, devoid of editorial slant. This experience has been a highly cherished one -- one that has placed the writer in intimate contact with his fellow members and with the growth of their activities in many parts of the world....In signing off, your reporter wishes to thank most sincerely for their indulgent cooperation the Editor of NEUROLOGY, Russell N. DeJong; its Publisher, Louis M. Cohen; and its Managing Editors, first Margaret Kane and, more recently, Belle Rockwood. He also wishes to express gratitude and appreciation to all AAN fellow members for their interest and support.

Percival Bailey


FOR ELECTRODIAGNOSIS IN NEUROMUSCULAR DISEASE AND TRAUMA
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This new compact instrument includes sensitive high gain amplifiers with new simplified calibrator, loudspeaker, flat-face seven inch cathode ray tube, a versatile synchronized stimulator for conduction time tests and everything necessary to make electronically synchronized, ten second Polaroid® records of all tests with push-button simplicity.

The new Model B includes electronic circuitry of proven success in the TECA TE Series console electromyographs. The amplifiers have excellent artifact rejection, wide frequency response, and include an effective powerline artifact rejection filter. The new nerve conduction velocity facilities include **time marker pulses** superimposed electronically on the recording beam. This permits accurate direct measurements of conduction time. Conduction velocity testing is further simplified by the unique **new stimulator electrode** which now contains the stimulus intensity control. This expedites testing when working without assistance. Adjustment of stimulus pulse duration, rate and delay permit a wide range of testing applications.

A new rigid mount positions the camera away from the operator when not in use and permits rapid positioning of the camera for recording. The camera mount serves as a convenient carrying handle when transporting the electromyograph.

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The TECA TE-Series Electromyographs are of modular design for maximum versatility. One or two channel models contain integral two-channel magnetic tape recorders. Special multi-trace photorecording features and direct reading time indicators are available with this series.

Because it sustains relief of myasthenia gravis symptoms up to two and one-half times as long as the regular tablet, new MESTINON TIMESPAN often "eliminates the need for sleep interruption to take further medication and leads to better strength in the morning."* For treatment during waking hours, MESTINON TIMESPAN offers greater convenience, prolonged relief on fewer individual doses, and unprecedented freedom from muscarinic side effects.

DOSAGE: Timespan tablets – ½ to 3 tablets once or twice daily.

HOW SUPPLIED: Tablets, 180 mg each – bottle of 100.

*K. R. Magee and M. R. Westerberg, **Neurology, 9**:348, 1959.

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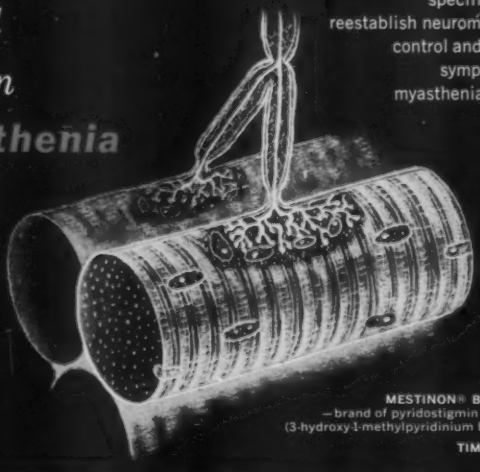
Schematic drawing of nerve endings in striated muscle tissue. By inhibiting destruction of acetylcholine at this junction, Mestinon acts specifically to reestablish neuromuscular control and relieve symptoms of myasthenia gravis.



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"PANTOPAQUE" *is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iophendylate Injection, U.S.P., by Lafayette Pharmacal Inc. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*

THERAPEUTIC INDEX

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IN EPILEPSY

Indications: In the control of grand mal and psychomotor seizures.

Usual Dosage: *Patients receiving no other anticonvulsants—Adults and Children (over 8 years):* 1 tablet (0.25 Gm.) daily (preferably at bedtime) for 1 week. Increase by 1 tablet daily each week, until control. Dosage exceeding 2 Gm. daily presently not recommended. *Children under 8 years:* Order of dosage same as for adults, but start with ½ tablet (0.125 Gm.) daily and increase by ½ tablet daily each week, until control. (Where a smaller starting dose is required, use 50 mg. tablet.)

Patients already receiving other anticonvulsants—Adults and Children (over 8 years): 0.25 Gm. daily, and gradually increased while the dosage of the other drug(s) is gradually decreased. Continued until satisfactory dosage level is achieved for combination, or until other medication is completely withdrawn. *Children under 8 years:* Initially one-half the adult dose, or 0.125 Gm. daily. Gradual increases and decreases as described in adult regimen. (Where a smaller starting dose is required, use 50 mg. tablet.)

When therapy with "Mysoline" alone is the objective, the transition should not be completed in less than two weeks.

Precautions: Side reactions, when they occur, are usually mild and transient, tending to disappear as therapy is continued or as dosage is adjusted. Commonly reported side effects are drowsiness, ataxia, vertigo, anorexia, irritability, general malaise, nausea and vomiting. No serious irreversible toxic reactions have been observed. (Occasionally, megaloblastic anemia has been reported in patients on "Mysoline." The condition is readily reversible by folic acid therapy, 15 mg. daily, while "Mysoline" is continued.) As with any drug used over prolonged periods of time, it is recommended that routine laboratory studies be made at regular intervals.

Supplied: No. 3430—"Mysoline" Tablets—Each scored tablet contains 0.25 Gm. (250 mg.) of Primidone, in bottles of 100 and 1,000. No. 3431—"Mysoline" Tablets—Each scored tablet contains 50 mg. of Primidone, in bottles of 100 and 500.

Also available: No. 3850—"Mysoline" Suspension—Each 5 cc. (teaspoonful) contains 0.25 Gm. of Primidone, in bottles of 8 fluidounces.

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Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS*—400 mg. *unmarked*, coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).
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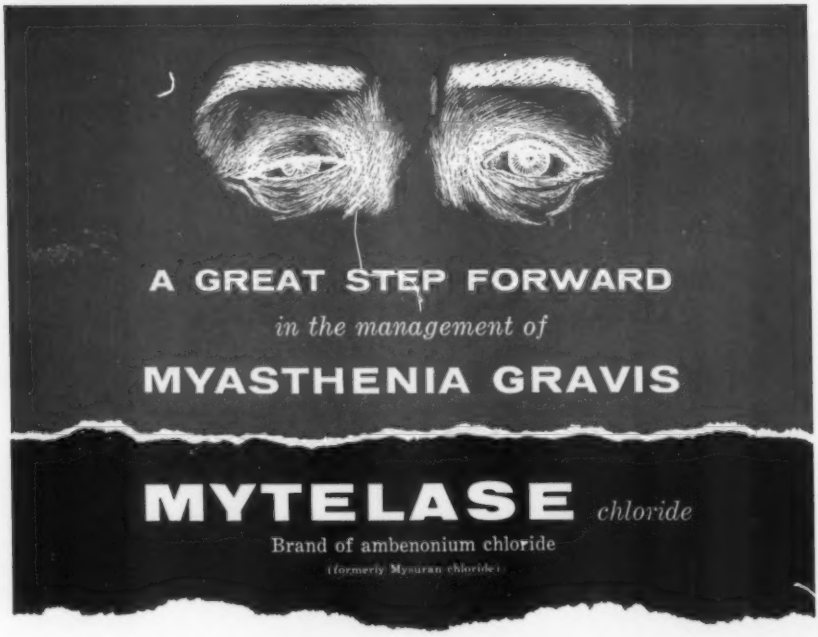

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Patients "... feel better, are stronger, and are closer to their normal health."[1]

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Write for booklet discussing in detail clinical experience, dosage, side effects and precautions to be observed.

1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

Mytelase, trademark

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